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VICE PRESIDENT
CHEMSTAR

June 22, 1998

U.S. Environmental Protection Agency
Office of Pollution Prevention and Toxics
Document Control Office (7407)
Room G-099
401 M Street, S.W.
Washington, D.C. 20460

Re: TSCA Docket No. OPPTS-42187A; FRL 4869-1
61 Fed. Reg. 33178 (June 26, 1996); 62 Fed. Reg. 67466 (Dec. 24, 1997);
63 Fed. Reg. 5915 (Feb. 5, 1998); 63 Fed. Reg. 19694 (Apr. 21, 1998).

Dear Sir or Madam:

The Hydrogen Fluoride HAPs Testing Task Group (HF HAPs Group) of the Chemical Manufacturers Association (CMA) is pleased to submit the attached comments on EPA's proposed test rule for hazardous air pollutants. The HF HAPs Group is in negotiations with EPA to enter an Enforceable Consent Agreement for testing of HF. We are hopeful that we will be able to reach agreement on a testing program *in lieu* of the proposed test rule. However, since EPA and the HF HAPs Group have not yet reached agreement on the alternative testing program, we are submitting these comments on the test rule as proposed (including amendments to the original proposal). The HF HAPs Group also incorporates by reference the general comments being submitted separately by CMA.

If you have any questions concerning these comments or would like additional information, please call Elizabeth Festa Watson, Manager of the HF HAPs Group, at (703) 741-5629.

Sincerely yours,

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CONTAINS NO CBI

BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION HYDROGEN FLUORIDE HAPs TESTING TASK GROUP ON EPA's PROPOSED TEST RULE FOR HAZARDOUS AIR POLLUTANTS

Proposed Test Rule for Hazardous Air Pollutants; Proposed Rule, as Amended, 61 Fed. Reg. 33178 (June 26, 1996); 62 Fed. Reg. 67465 (Dec. 24, 1997); 63 Fed. Reg. 5915 (Feb. 5, 1998); 63 Fed. Reg. 19694 (Apr. 21, 1998).	TSCA Docket No. OPPTS-42187A; FRL-4869-1

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EXECUTIVE SUMMARY

The Chemical Manufacturers Association (CMA) Hydrogen Fluoride HAPs Testing Task Group ("HF HAPs Group" or "Group") submits these comments in response to EPA's proposal to require inhalation testing for hydrogen fluoride (HF) under Section 4 of the Toxic Substances Control Act (TSCA), as part of a testing initiative for compounds listed as hazardous air pollutants (HAPs) under the Clean Air Act. 61 Fed. Reg. 33178 (June 26, 1996); 62 Fed. Reg. 67465 (Dec. 24, 1997); 63 Fed. Reg. 5915 (Feb. 5, 1998); 63 Fed. Reg. 19694 (Apr. 21, 1998). The HF HAPs Group supports and incorporates by reference the comments filed by CMA on general issues associated with the proposed test rule. The comments herein address issues specific to EPA's testing proposal for HF, and raise the following key points:

- The HF HAPs Group supports the steps EPA has taken to facilitate and encourage constructive dialogue on the proposed test rule. The Group has taken advantage of this process by meeting with the Agency and submitting an alternative testing proposal. EPA has responded to the alternative testing proposal and the HF HAPs Group has submitted comments on EPA's response. An initial meeting to negotiate an Enforceable Consent Agreement (ECA) was held on February 5, 1998, and scientists from EPA and the Group have engaged in subsequent discussions concerning testing protocols. We are hopeful that we will be able to reach agreement on a testing program *in lieu* of the proposed test rule. Nevertheless, since EPA and the HF HAPs Group have not yet reached agreement on the alternative testing program, we are submitting these additional comments on the test rule as proposed.

- EPA has stated that it intends to use the data from this rulemaking primarily to support its residual risk determinations for hazardous air pollutants under Section 112 of the Clean Air Act. Accordingly, the HF HAPs Group believes strongly that EPA should require only that testing which is necessary for conducting residual risk assessments and should explain more fully how the test data will be used. It is inappropriate for EPA to require approximately $3 million in testing for HF when the Agency has not yet determined how it will conduct residual risk determinations, and therefore how it will use the test data, if at all.

- EPA should reconsider the specific testing requirements proposed for HF.

  - Existing acute data are more than adequate to assess any risks from accidental releases. Acute inhalation studies exist in rats, mice, guinea pigs, rabbits, dogs, and humans. These studies have tested for a variety of sensitive endpoints, including many of the endpoints for which EPA has proposed testing. The results of these tests have been used to develop comprehensive standards and guidelines to prevent HF releases and to minimize the impact of any accidental releases which do occur.

  - Testing for respiratory sensory irritation is not needed because existing data are available and have been submitted to EPA. In addition, the National Advisory

Committee has found the existing data base sufficient to establish Acute Exposure Guideline Levels (AEGLs) for HF.

- The biological chemistry of HF indicates that the fluoride ion is responsible for potential systemic toxicity from exposures to HF. Accordingly, oral toxicity studies with sodium fluoride reasonably can be used to predict the potential toxicity of HF.

- A subchronic HF inhalation study exists, as well as subchronic sodium fluoride studies. The HF HAPs Group believes these studies are sufficient to conduct residual risk assessments for HF.

- The developmental and reproductive toxicity of HF can be predicted from existing sodium fluoride studies.

- The HF HAPs Group believes a neurotoxicity test battery using EPA guidelines is unnecessary. The findings from a detailed neurotoxicity study on sodium fluoride administered in drinking water to rats (Mullenix, 1995), as well as relevant animal data from several standard toxicology studies on HF, demonstrate the absence of pathological effects on brain tissue and the absence of clinical signs suggestive of neurotoxicity.

- Data from repeated dose studies on HF and inorganic fluorides, as well as epidemiological studies of communities with fluoridated water supplies, indicate that fluorides do not produce immunotoxic effects. Therefore, additional testing for immunotoxicity is not necessary.

- At a minimum, EPA should adopt an iterative approach to testing for HF, as recommended by the National Academy of Sciences, rather than requiring an extensive and unnecessary data set for HF.

- The HF HAPs Group supports the comments being submitted by CMA concerning the health effects test guidelines that EPA proposes to apply to testing under this test rule.

- As a legal matter, EPA has not presented sufficient data and analysis to support the findings required by Section 4 of TSCA for HF.

  - EPA has not shown that insufficient data exist for the Agency to make its residual risk determinations for HF, or that all of the proposed testing for HF is necessary to enable EPA to make such determinations. Nor has EPA demonstrated that the proposed testing is necessary to support an assessment of the potential hazards associated with accidental releases. In the latter context, an emergency release standard has already been established for HF.

  - EPA has not presented adequate justification to support its "A" finding for HF. EPA has not correlated HF's suspected toxicity with anticipated levels of

exposure as specifically required by the appellate court's decision in *Chemical Manufacturers Association v. EPA*, 859 F.2d 977, 983 (D.C. Cir. 1988). EPA also has improperly used "A" findings for three endpoints (respiratory toxicity, liver toxicity and eye irritation) to require testing for other, unrelated endpoints, such as developmental and reproductive toxicity. The HF HAPs Group believes EPA's approach contravenes the clear intent of Congress to authorize EPA to require testing under Section 4(a)(1)(A) only to the extent EPA finds that a chemical "may present an unreasonable risk" of injury to human health or the environment. A showing of an unreasonable risk of respiratory toxicity is not a showing of an unreasonable risk of developmental toxicity.

- EPA's "B" finding for HF rests on worker exposures and releases to the environment. Worker exposures are not relevant for determining whether testing is necessary to assess residual risks to the general population from environmental releases of HAPs and therefore should not be used as a basis for requiring testing in a TSCA Section 4 test rule for HAPs. With respect to the quantities of HF released to the environment, EPA has made no attempt to estimate the levels of exposure that result from these releases. Accordingly, EPA has not adequately supported its "B" finding for HF.

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INTRODUCTION

The Chemical Manufacturers Association (CMA) Hydrogen Fluoride HAPs Testing Task Group ("HF HAPs Group" or "Group") submits these comments in response to EPA's proposal to require inhalation testing of hydrogen fluoride (HF) under Section 4 of the Toxic Substances Control Act (TSCA), as part of a testing initiative for compounds listed as hazardous air pollutants (HAPs) under the Clean Air Act, as amended. 61 Fed. Reg. 33178 (June 26, 1996); 62 Fed. Reg. 67465 (Dec. 24, 1997); 63 Fed. Reg. 5915 (Feb. 5, 1998); 63 Fed. Reg. 19694 (Apr. 21, 1998). The HF HAPs Group consists of major U.S. producers of HF as well as importers, exporters, and processors of HF.[1] The HF HAPs Group supports and incorporates by reference the comments filed by CMA on general issues associated with the proposed test rule. The comments herein address issues specific to EPA's testing proposal for HF.

EPA has proposed the following inhalation studies for HF: acute toxicity with histopathology and appraisal of respiratory sensory irritation, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, and immunotoxicity. 62 Fed. Reg. at 67484. According to EPA, the primary purpose of this testing initiative is to provide data on HAPs that will be needed for residual risk assessments following installation of maximum achievable control technology (MACT) pursuant to Section 112 of the Clean Air Act. EPA's notice also solicited proposals for pharmacokinetics studies that could be used to extrapolate oral data to predict risk from inhalation.

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1 The Hydrogen Fluoride HAPs Testing Task Group is a separately-funded Task Group under the CMA Hydrogen Fluoride Panel. Members of the Group include 3M Specialty Materials Division, AlliedSignal Inc., Aluminum Company of America (ALCOA), Chemtech Products, Inc., Dupont FluoroProducts, Elf Atochem North America, Inc., HCI Chemicals (USA), LaPorte Fluorides, LCI/Norfluor, Nissho Iwai American Corp., Quimica Fluor, S.A., Seimens Power Corp., Solvay Fluorides, Inc., and Tessenderlo-Kerley, Inc.

The HF HAPs Group believes that not all testing proposed by EPA is necessary because significant data already exist for HF and sodium fluoride.[2] On November 22, 1996, we submitted a proposal for alternative testing to EPA, including pharmacokinetics testing.[3] Under the proposal, a physiologically-based pharmacokinetic (PBPK) model would be developed and would be used to extrapolate existing oral toxicity data for sodium fluoride to determine the potential for neurotoxic, developmental, and reproductive effects due to inhalation of HF. The proposal also included conduct of a subchronic (28-day) inhalation study.[4] The Alternative Testing Proposal cited existing data as being sufficient to meet acute toxicity testing needs, and proposed that immunotoxicity testing was unnecessary, for reasons set forth in the Alternative Testing Proposal.

EPA responded to the Alternative Testing Proposal by letter dated June 26, 1997.[5] As a preliminary position, EPA indicated that the proposal would provide adequate data for route-to-route extrapolation of developmental and reproductive effects, but that EPA believes neurotoxicity and immunological testing are needed. EPA noted that the proposal does not address how the second species developmental testing requirement identified in the proposed rule

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2 The HF HAPs Group provides detailed information on the available toxicity data for HF and sodium fluoride in Appendix I.

3 *Proposal for a Physiologically-Based Pharmacokinetics (PBPK) Model for Hydrogen Fluoride* (Nov. 22,1996) [Alternative Testing Proposal] (attached as Appendix II). The proposal was submitted by the CMA Hydrogen Fluoride Panel. Since then, the Hydrogen Fluoride HAPs Testing Task Group was created as a separately-funded Task Group of the Hydrogen Fluoride Panel. The HAPs Testing Task Group (*see* note 1, above) is the entity that is participating in the negotiations for an Enforceable Consent Agreement (ECA).

4 The Alternative Testing Proposal did not specify the length of the subchronic study. The intent to conduct a 28-day study was clarified in a subsequent letter, discussed below. *See* note 6, below.

5 Letter from Charles M. Auer, Director, Chemical Control Division, to Elizabeth Festa Watson, Manager, Hydrogen Fluoride Panel (June 26, 1997) [EPA June 26 Response] (attached as Appendix III).

would be met. EPA also indicated a need for an acute inhalation macrophage function assay in addition to the existing data cited by the HF HAPs Group, and stated the inhalation study should be for a 90-day period.

The HF HAPs Group submitted a reply to EPA's response, indicating the Group's interest in pursuing an ECA, and discussing some issues for which further discussions would be necessary to ensure there is common understanding regarding the extent of necessary testing.[6] On February 5, 1998, EPA and the HF HAPs Group had an initial meeting to negotiate an ECA. Based on EPA's response to the Alternative Testing Proposal, the February 5 meeting, and subsequent communications between members of the Group and EPA, the HF HAPs Group believes that a mutually agreeable alternative testing ECA can be reached. However, since the ECA negotiations are not complete, and as suggested by EPA in its June 26 Response, the HF HAPs Group is submitting these additional comments on the test rule as proposed.

In Part I of these comments, the HF HAPs Group provides an overview of the proposed rule. In Part II, the HF HAPs Group expresses its support for steps EPA has taken to facilitate and encourage constructive dialogue on the proposed rule. The HF HAPs Group has taken advantage of opportunities to meet with the Agency, and, as described above, has in good faith submitted an Alternative Testing Proposal.

Part III shows why EPA should require only that testing which is necessary to conduct residual risk assessments under the Clean Air Act, and should explain more fully how the test data will be used. The HF HAPs Group believes that it is inappropriate for EPA to

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6 Letter from Courtney M. Price, Vice President, CHEMSTAR, to Charles M. Auer, Director, Chemical Control Division (Sept. 10, 1997) [HF HAPs Group Sept. 10 Reply] (attached as Appendix IV).

require more than $3 million in testing for HF (which the Group believes would be the true cost of the proposed testing) when the Agency has not yet determined how it will conduct residual risk determinations, and therefore how it will use the test data.

In Part IV, the HF HAPs Group addresses the specific testing requirements proposed for HF. The HF HAPs Group believes the testing proposed by EPA is not necessary to support residual risk assessments for HF, nor is the testing necessary to assess potential hazards associated with any accidental releases. Existing acute data are more than adequate to assess any risks from accidental releases. Acute inhalation studies exist in rats, mice, guinea pigs, rabbits, dogs, and humans. These studies have tested for a variety of sensitive endpoints, including many of the endpoints for which EPA has proposed testing. Testing for respiratory sensory irritation is not needed because such data exist and have been submitted to EPA. Indeed, the National Advisory Committee has used these published data to propose Acute Exposure Guideline Levels (AEGLs) for HF.

In Part IV, the Group also explains that the fluoride ion is responsible for potential systemic toxicity from exposures to HF. Accordingly, studies on sodium fluoride reasonably can be used to predict the toxicity of HF. A 90-day subchronic HF inhalation study exists. That study, coupled with subchronic sodium fluoride studies, is adequate to conduct residual risk determinations for HF. Similarly, the developmental and reproductive toxicity of HF can be predicted from existing sodium fluoride studies.

In Part IV, the HF HAPs Group further shows that neurotoxicity testing should not be required because existing data on sodium fluoride are adequate. Conducting neurotoxicity testing using EPA guidelines would not improve the quality of information that is already

available, and no additional neurotoxicity testing is necessary to conduct residual risk determinations for HF. Moreover, data from repeated dose studies on HF and inorganic fluorides, as well as epidemiological studies of communities with fluoridated water supplies, indicate that fluorides do not produce immunotoxic effects, and therefore, additional testing is not necessary.

The Group then explains in Part IV that, at a minimum, EPA should adopt an iterative approach to testing, as recommended by the National Academy of Sciences, rather than requiring an extensive and unnecessary data set for HF. Finally, the HF HAPs Group supports the comments being submitted by CMA to this docket concerning the health effects test guidelines.

In Part V, the HF HAPs Group demonstrates that, as a legal matter, EPA has not presented sufficient data and analysis to support the findings required by Section 4 of TSCA. EPA has not shown that insufficient data exist for the Agency to make its residual risk determinations for HF, or that the proposed testing for HF is necessary to enable EPA to make such determinations. Moreover, EPA has not provided adequate justification to support its "A" finding for HF. EPA has not correlated HF's suspected toxicity with anticipated levels of exposure, as expressly mandated in a previous court decision under TSCA Section 4. EPA also has improperly used "A" findings for three endpoints to require testing for other, unrelated endpoints. Finally, EPA's "B" finding for HF rests on worker exposures, which are not relevant for determining whether testing should be required to assess residual risks to the general population. EPA has not attempted to assess likely levels of general population exposure to HF. Accordingly, EPA has not adequately supported its "B" finding for HF.

I. OVERVIEW OF PROPOSED RULE

The proposed rule, as amended, includes 20 compounds. EPA proposes to require "Option Three" level testing for all compounds included in the test rule. 61 Fed. Reg. at 33182. Option Three includes inhalation studies to address the following endpoints (to the extent data are not already available): acute toxicity (with histopathology), respiratory sensory irritation, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, immunotoxicity, mutagenicity and, where concern is indicated by results of mutagenicity studies or other test data, carcinogenicity.

EPA has proposed the following testing for HF: acute toxicity, respiratory sensory irritation, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, and immunotoxicity. 62 Fed. Reg. at 67484. EPA estimates that this testing will cost about $2.5 million. 62 Fed. Reg. at 67478. However, because of the necessity for employing special inhalation chambers for toxicity testing and implementing appropriate safety measures for handling HF in a laboratory, EPA may have underestimated significantly the costs. Such safety and handling costs typically are about fifteen percent of the total study costs. Therefore, the HF HAPs Group believes a more realistic estimate for conducting the EPA proposed studies with HF is about $3 million.

All compounds, including HF, were selected for inclusion in the HAP test rule primarily based on releases to air as reported in the 1993 Toxics Release Inventory (TRI) database under the Emergency Planning and Community Right-to-Know-Act (EPCRA). 61 Fed. Reg. at 33184. All chemicals selected for inclusion in the test rule had reported air emissions above 50 tons in 1993. *Id.* EPA did not conduct any air dispersion modeling exercises to

estimate likely human exposures from these releases, although the Agency has previously conducted such modeling exercises to support rulemakings under the Clean Air Act.[7]

EPA has based its proposed testing requirements for HF on findings under TSCA Section 4(a)(1)(A) (chemicals that may present an unreasonable risk of injury to health and the environment) based on its potential to induce respiratory toxicity, liver toxicity and skin and eye irritation, and Section 4(a)(1)(B) (chemicals that enter the environment in substantial quantities or to which there may be significant or substantial human exposure), based on reported worker exposures and releases to the environment.[8] The Agency also purports to find that existing HF data are "insufficient" to predict the effects of HF on human health and the environment, and that the proposed testing is "necessary" to support EPA's risk management and risk assessment functions.[9]

The preamble to the original proposed rule indicates that the primary use of the test data will be to support residual risk determinations under Section 112(f) of the Clean Air Act.[10] 61 Fed. Reg. at 33179-80. The Clean Air Act requires EPA to promulgate technology-based standards that require the maximum degree of HAP emission reductions achievable for a source category. CAA § 112(d). Section 112(f) requires EPA to establish any additional standards that are necessary to protect public health and the environment with an "ample margin

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7 For example, EPA conducted air dispersion modeling exercises to propose "high risk" HAPs under the Early Reduction program, 57 Fed. Reg. 61970 (Dec. 29, 1992), and to propose *de minimis* emission levels of HAPs under the Section 112(g) Construction/Reconstruction program, 59 Fed. Reg. 15504, 15526 (Apr. 1, 1994).

8 EPA, *TSCA Section 4 Findings for 21 Hazardous Air Pollutants (Draft)* 46-49 (Mar. 31, 1996) [TSCA Section 4 Findings].

9 *Id.* at 49-52.

10 EPA also indicates that the data will be used to evaluate risks associated with accidental releases of test compounds under CAA Section 112(r).

of safety," and to ensure an excess cancer risk of no greater than one in one million. CAA § 112(f)(2). EPA is required to make these "residual risk" determinations only for categories or subcategories of sources that include at least one "major source" of HAPs.[11]

The EPA June 26 Response to the HF HAPs Group's Alternative Testing Proposal underscores that the intent of the test rule is to support residual risk determinations. EPA therein states:

> The testing requirements for HF in the proposed HAPs test rule were identified by EPA for the purpose of providing a database to permit the assessment of residual risk following the implementation of the maximum achievable control technology (MACT) standards required by the Clean Air Act.[12]

Thus, these comments address the proposed testing needs in light of residual risk needs. While the HF HAPs Group appreciates EPA's constructive dialogue on technical issues, it believes EPA has not explained how the results from the proposed HAP test rule will be used to support the residual risk efforts.

II. THE HF HAPS GROUP SUPPORTS EPA'S EFFORTS TO PROMOTE A CONSTRUCTIVE DIALOGUE ON ISSUES ASSOCIATED WITH THE PROPOSED RULE

The HF HAPs Group supports the steps EPA has taken to facilitate and encourage constructive dialogue on the scientific issues presented by its proposed HAP test rule. These steps have included: (1) initially allowing 180 days for public comment on the proposed rule, which is longer than EPA has provided for comment on most other TSCA testing proposals; (2) scheduling a public meeting to encourage early dialogue on technical and policy issues; (3)

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11 See CAA § 112(f)(5). The Clean Air Act defines the term "major source" to include any facility that emits or has the potential to emit 10 tons/year of a single HAP or 25 tons/year of any combination of HAPs. *See* CAA § 112(a)(1).

12 EPA June 26 Response at 2.

inviting alternative testing proposals, focusing primarily on approaches that might allow use of existing oral data in lieu of conducting new studies by inhalation; (4) setting an early deadline for the submission of those proposals, and committing to providing feedback during the comment period; and (5) extending the comment period to ensure EPA feedback was provided prior to the end of the public comment period. All of these steps have facilitated constructive dialogue on technical issues.

The HF HAPs Group has utilized the opportunities provided by EPA. The Group met with the Agency on the second day of public meetings to address various issues associated with HF. Furthermore, although the HF HAPs Group does not believe that any testing of HF is necessary to support residual risk analyses, it has submitted an Alternative Testing Proposal that it believes will be adequate to meet any legitimate testing needs and is more cost-effective than the testing identified in the proposed rule.

Based on the EPA June 26 Response to the testing proposal and the February 5 ECA negotiation meeting, the HF HAPs Group is hopeful of reaching an agreement with the Agency on an alternative testing program for HF. The HF HAPs Group appreciates the steps EPA has taken to foster an open, cooperative dialogue on the HAP testing initiative, and hopes that an agreement can be reached on the appropriate scope of testing for HF. Because ECA negotiations have not yet been completed, however, the HF HAPs Group submits the following comments on the HF testing requirements that were proposed on June 26, 1996, as amended on December 24, 1997, on February 5, 1998, and on April 21, 1998.

III. EPA SHOULD EXPLAIN MORE FULLY HOW THE TEST DATA WILL BE USED

As discussed above (Part I), the primary purpose of the HAP testing initiative is to support residual risk analyses under the Clean Air Act. EPA's residual risk determinations involve an examination of whether emissions reductions achieved under technology-based MACT standards are sufficient to ensure that the public is protected from adverse health effects with an "ample margin of safety." CAA § 112(f)(2)(A). However, EPA has not explained how the data obtained under this testing initiative will be used to support its activities under the Clean Air Act residual risk provisions.[13]

CAA Section 112(f) directed EPA to submit a report to Congress by November 15, 1996, that would address, among other topics, "(A) methods of calculating the risk to public health remaining, or likely to remain, from sources subject to regulation under [section 112] after the application of [MACT] standards; [and] (B) the public health significance of such estimated remaining risk . . . ." 42 U.S.C. §§ 7412(f)(1)(A) & (B). This report, however, had not been developed at the time EPA proposed the HAP test rule. In fact, the draft report was announced only in April 1998, one day after the latest amendments to the proposed HAP test rule.[14]

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13 EPA claims that the data also will be used to support implementation of "several" other provisions of Clean Air Act Section 112, including estimation of risks associated with accidental releases (Section 112(r)) and delisting determinations (Section 112(b)(1)). 61 Fed. Reg. at 33179. The non-acute tests proposed by EPA are not relevant for purposes of Section 112(r). Moreover, EPA has not taken any initiative to pursue HAPs delistings in the absence of petitions from industry that include extensive supporting documentation. Nor is the HF HAPs Group aware of any other provisions of Section 112 for which the proposed data would be useful. Thus, it is clear that EPA intends to utilize this data primarily to support residual risk determinations, as EPA confirmed in its June 2 Response. *See* text accompanying note 12, above.

14 EPA, *Draft Residual Risk Report to Congress* (Apr. 14, 1998); announced at 63 Fed. Reg. 19914 (April 22, 1998).

At no time has EPA articulated how the results from the HAP test rule will be used to support its residual risk efforts. Indeed, the *Draft Residual Risk Report to Congress* supports the conclusion that much the proposed testing in fact may not be necessary for the residual risk effort. For example, EPA states in the draft report that, in general, "[t]he minimum database for the development of an RfC [reference concentration] is one well-conducted subchronic study that evaluated the respiratory tract and identified a NOAEL [No Observed Adverse Effect Level]."[15] EPA goes on to state that other types of studies can increase confidence in the RfC, but does not state that such studies are necessary to develop an RfC for residual risk analysis. In fact, EPA indicates that, even where there is insufficient data for an RfC, EPA will conduct residual risk assessments using available data.[16] Thus, the draft report implicitly acknowledges that for at least some compounds additional testing may not be necessary to conduct residual risk analyses, much less the full array of tests proposed here.[17]

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15 *Draft Residual Risk Report to Congress* at 51.

16 *See Draft Residual Risk Report to Congress* at 50:

> For chronic non-cancer and cancer criteria, the preferred source is EPA's Integrated Risk Information System (IRIS). . . . Other chronic consensus toxicity criteria that have undergone less rigorous internal Agency review are available in HEAST, the Health Effects Assessment Summary Tables, which will be consulted for residual risk assessments when data are unavailable in IRIS. For HAPs not having adequate toxicity information in IRIS or HEAST, EPA will develop and follow a hierarchy of data sources, including various kinds of Agency health effects assessment documents, ATSDR toxicity profiles, and other sources.

17 We do not mean to imply that values in IRIS or HEAST for any particular compound provide a sufficient basis for assessing health risks. Indeed, it is well-known that IRIS and HEAST suffer from deficiencies and contain many outdated values. When performing residual risk assessments, EPA may not rely exclusively on these values, but must consider whatever additional information is submitted by interested parties. *See* OAQPS "Guidance on Use of Integrated Risk Information System (IRIS) Values" (August 26, 1994). However, when a valid, current RfC exists or may be derived from available data, and ambient concentrations are determined to be below the RfC, clearly no further testing should be necessary since the RfC, by

Perhaps this is why EPA's proposal lists several "secondary" uses of data.[18] The mere fact that data might be useful in another context, however, is not sufficient to support a test rule under TSCA. The proposed HAP test rule, as its name indicates, is designed to provide data that will be used by the Agency to support its activities under the Clean Air Act. The mention of secondary uses of the data cannot serve as an excuse to require testing that is not necessary to implement the requirements of Clean Air Act Section 112. *See* Section V.B., below.

Accordingly, it is inappropriate for EPA to require $3 million in testing for HF, unnecessarily using hundreds of laboratory animals, when the Agency has not yet determined how the data will be used. Before requiring such extensive testing, the HF HAPs Group believes EPA should have a clear understanding of how residual risk analyses will be conducted, and, in particular, how the specific studies included in the HAP testing proposal for each compound will be used to support such an effort. Otherwise, there is a significant potential for large amounts of money and substantial numbers of laboratory animals to be wasted on testing that is not necessary to evaluate the risks to human health and environment from the environmental releases of HF.

Moreover, any testing requirements for HF should not be dictated by an abstract desire to create a uniform toxicity data base for HAPs generally, but instead should reflect a

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EPA's definition, represents a concentration to which even a sensitive individual may be exposed for a lifetime without adverse effect. *See* EPA Office of Research and Development, "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry," EPA No. 600/8-90/099F (October, 1994).

18 EPA cites the following "secondary" uses of the data: (1) helping to inform communities and citizens of toxic chemical hazards in their communities; (2) assisting other agencies in assessing chemical risks; (3) assisting EPA in evaluating chemical delisting petitions and other regulatory decisions under other Agency programs; (4) assisting state and local authorities in setting standards; (5) supporting assessments of "burst" exposures; and (6) improving the data and data confidence contained in the IRIS database. 61 Fed. Reg. at 33180.

chemical-specific evaluation of HF. EPA's insistence on "Option Three" level testing for all compounds in the proposed rule cannot be justified given that the available toxicity data, the potential for inhalation exposure, and the resultant need for inhalation data vary significantly among the chemicals. Indeed, EPA's imposition of extensive test requirements under this test rule is arbitrary, given that it appears only some of the HAPs will be subject to a test rule. Therefore, the concept of a uniform data base is a chimera. This issue is discussed further in the comments being submitted by CMA on general issues.

Accordingly, the HF HAPs Group believes that EPA should consider more carefully the extent to which additional data are needed to support the Agency's risk assessment and risk management functions. Following such an evaluation, and depending on the outcome of EPA's final report to Congress, the Agency may ultimately conclude, as the HF HAPs Group already believes, that the proposed testing for HF in fact is not necessary to support residual risk assessments under the Clean Air Act.

IV. EPA SHOULD RECONSIDER ITS PROPOSED TESTING REQUIREMENTS FOR HF

For the reasons discussed below, the HF HAPs Group believes that the testing proposed by EPA is not necessary to support residual risk assessments for HF, nor is it necessary to assess potential hazards associated with any accidental releases. Existing acute data are more than adequate to assess any risks from accidental releases. Furthermore, because the fluoride ion is responsible for potential systemic toxicity from exposures to HF, the extensive toxicity database for sodium fluoride reasonably can be used to predict the chronic toxicity of HF. Accordingly, additional testing simply is not necessary.

The HF HAPs Group is providing detailed comments on the available toxicity data for HF and sodium fluoride in Appendix I. The HF HAPs Group's Alternative Testing Procedure is provided in Appendix II.[19] The detailed comments in Appendix I, in conjunction with the alternative testing strategy proposed by the HF HAPs Group (Appendix II), demonstrate the large body of data available for HF from which a determination of residual risk can be made. These appendices explain in more detail the results of the studies described below.

A. Acute Inhalation and Respiratory Sensory Irritation

EPA proposes to require that HF be tested using the Acute Inhalation Toxicity with Histopathology Test Guideline (40 C.F.R. § 799.9135) to study the acute sublethal effects of HF, especially effects on the respiratory system associated with accidental release and acute exposures. The test guideline is designed primarily to assess two endpoints: (1) histopathology of the respiratory tract, kidney, liver, and other target organs; and (2) cell damage via lung lavage.

EPA justified its proposed acute testing for HF by stating that, although several acute HF studies exist, these studies are inadequate because in some cases only one sex was tested, while in others there was inadequate exposure duration, only limited endpoints were assessed, or the study was insufficiently reported. 61 Fed. Reg. at 33192; TSCA Section 4 Findings at 49-50. However, the mere fact that each existing acute study is not "perfect" -- or in some way does not conform exactly to the latest revisions in EPA's testing guidelines -- is not a sufficient basis to reject those studies entirely and require additional testing. By such a measure,

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19 This document was submitted previously to EPA in response to EPA's invitation in the proposed rule for proposals of pharmacokinetics studies that would permit route-to-route data extrapolation.

almost all previous studies would have to be disregarded, which is surely not EPA's intent in issuing new testing guidance.[20] Instead, the relevant question should be whether the existing acute studies in the aggregate, coupled with other information about toxicity and physical/chemical properties, are adequate to characterize the chemical's acute toxicity under reasonably foreseeable exposure scenarios. The HF HAPs Group believes that this clearly is the case with respect to HF, and no additional acute testing is necessary.

The results of existing HF acute inhalation studies sufficiently characterize an exposure-response relationship for sensitive endpoints following acute HF exposure. Existing acute HF studies have included blood analyses, bronchoalveolar lavage fluid analyses to evaluate cytological and biochemical parameters, pulmonary function tests, organ weight measurements, and histopathological examination of the respiratory tract and other major organs. Additionally, acute inhalation studies in several animal species characterize the toxicological responses (lethal and sublethal) to acute high exposures to HF, such as might be expected under accidental release scenarios. Some of these studies demonstrate evidence of regional deposition of inhaled HF at sites of contact, while other studies include histopathological examination to evaluate regeneration or repair of affected tissues after inhalation exposure to HF.

Acute inhalation HF studies have been conducted in rats, guinea pigs, rabbits, mice, and dogs. (Stonybrook, 1996; Dupont, 1990; Morris, 1979; Morris and Smith, 1982;

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20 *Compare* EPA's recent revisions to the TSCA Section 8(d) Health and Safety Reporting Rule, which requires file searches to go back to 1977, and reserves EPA's right to request even older studies. 63 Fed. Reg. 15765, 15773 (Apr. 1, 1998). In the preamble to the revised rule, EPA stated: "Over the years, commenters have suggested that file searches have resulted in considerable burden due to the reporting of some rather old studies which are less likely to meet current needs due to changing protocols to achieve state-of-the-art science and lack of application of Good Laboratory Practice Standards (GLPS). . . . However, limiting reporting of studies to only a certain time frame preceding the date of the listing of the substance could result in *useful studies* not being reported to EPA and ITC." 63 Fed. Reg. at 15770 (emphasis added).

Stavert *et al.*, 1991; Rosenholtz *et al.*, 1963; Machle *et al.*, 1934; Wohlslagel *et al.*, 1976; DiPasquale and Davis, 1971; Higgins *et al.*, 1972.) Data from existing studies of acute inhalation effects in humans have been used to recommend current emergency response planning guidelines for the protection of human health. (Machle *et al.*, 1934; Lee *et al.*, 1993; Largent, 1960; Lund *et al.* 1997.) A detailed discussion of these studies and their results can be found at Appendix I, pp. 1-10. Most of these studies were not referenced by EPA in its proposed rule and supporting documentation.

Thus, a review of the full range of available acute inhalation toxicity data and of more recent unpublished research on the effects of acute inhalation exposure to HF clearly shows that adequate toxicological data exists to estimate risks related to acute inhalation exposures to HF. In fact, both the Emergency Response Planning Committee of the American Industrial Hygiene Association and the National Advisory Committee for Acute Exposure Guideline Levels (AEGLs), sponsored by EPA, have utilized the existing acute toxicity data on HF to make recommendations for emergency response planning. (AIHA, 1991; Talmage, 1997.) Indeed, establishing these exposure limits for accidental releases represents a risk determination, so that EPA already has achieved the outcome for which it now proposes testing. In fact, the *Draft Residual Risk Report to Congress* indicates that AEGLs will be one of primary types of values used for acute effects assessment (p. 51). Accordingly, the HF HAPs Group believes that no additional acute inhalation testing is needed.

EPA also proposes to require a respiratory sensory irritation test using American Standard Test Method (ASTM) E 981-84 to provide a quantitative estimate of the sensory irritant potential of HF. 62 Fed. Reg. at 67484-85. The test detects irritation by a characteristic change

in the breathing pattern of mice, resulting in a reduction in the breathing rate during exposure to a test atmosphere. (ASTM, 1984.) This study is not necessary, because there exists a nucleus of acute inhalation toxicity data that can be used to estimate the adverse effects resulting from acute HF accidental exposures. Indeed, HF was assessed for sensory irritation potential in mice by ICI, with an estimated RD_{50} of 151 ppm. (CTL, 1990). The Panel has submitted this study to EPA. Moreover, the acute inhalation study in rats performed by Stonybrook Laboratory (1996) included several pulmonary function parameters and further characterizes the respiratory irritation potential of HF. In fact, the EPA National Advisory Committee for AEGLs has successfully used these data to make recommendations for guideline levels related to HF accidental releases and exposures. (Talmage, 1997.) Therefore, the HF HAPs Group believes that no additional respiratory sensory irritation testing of HF is needed.

B. Subchronic Toxicity

EPA proposes to require subchronic toxicity testing of HF using TSCA test guideline Section 799.9346. 62 Fed. Reg. at 67484-85. However, a 90-day inhalation study of HF, sponsored by EPA, already exists (Placke and Griffin, 1991). Although that study had some inadequacies, the HF HAPs Group believes that the Placke and Griffin study, coupled with existing data on sodium fluoride, is sufficient to characterize residual risks from exposure to HF, and therefore no further subchronic testing of HF is necessary.[21]

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21 Nonetheless, in light of the inadequacies in Placke and Griffin (1991), the Alternative Testing Proposal includes conduct of a study on the relationship between oral and inhalation exposure and the induction of systemic toxicity. *See* Appendix II. As part of that proposal, a study would be conducted to determine the concentration times time (CxT) relationship for HF over a period of 28 days, including periodic sacrifices for clinical pathology and pathology evaluations. These data and comparison with data developed from oral toxicity studies with sodium fluoride would provide a more complete characterization of the subchronic effects of the fluoride ion.

Studies on sodium fluoride provide relevant data because the chemistries of HF and of sodium fluoride in the body are such that, for either compound, the fluoride ion is the species of physiological interest. In transmembrane fluoride transport, non-ionic HF is the primary permeating species. (Whitford, 1983; Ekstrand, 1996.) This is true for all compartments of the body, *e.g.*, from lungs or skin into the blood or from the stomach into the blood. Thus, anhydrous HF inhaled into the lungs will cross the lung cell membrane as HF; sodium fluoride ingested into the stomach will cross the stomach cell membrane as HF.[22] Once absorbed into the tissues, however, the HF dissociates extremely rapidly to the fluoride ion.

The extent of ionization of HF in pure water (*i.e.*, when no buffers are present) is governed by its K_a (3.53×10^{-4}). The ratios of [HF]:[F] in 1.0 molar (M), 0.1 M and 0.01 M aqueous solutions of HF are approximately 52:1, 16:1 and 4:1, respectively. However, in the extracellular fluid in which buffers are present and the pH is 7.4, the degree of ionization of HF is governed by the Henderson-Hasselbach equation and the ratio of [HF]:[F] in the extracellular fluid is reversed in favor of fluoride ion and is approximately 1:9000. The ratio would be the same in the extracellular fluid whether HF or sodium fluoride were administered. Thus, fluoride contributed from HF is indistinguishable from fluoride contributed from sodium fluoride and will

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In the ECA negotiation process, EPA has continued to insist on 90-day inhalation study. To enable a successful ECA negotiation, the HF HAPs Group has indicated its willingness to conduct such a study under an ECA. However, the Group believes that, for HF, concentration is much more important than time, so that a 90-day test will provide little additional information than would be provided by a 28-day test.

22 At the site of entry or in contact with moisture in air, anhydrous HF instantaneously and strongly associates with water, forming hydrofluoric acid which is a weak acid and may not be fully ionized. Ingested sodium fluoride will be dissociated into sodium and fluoride ions. Some of the fluoride ions will associate with hydrogen ions to create HF that can then cross the cell membrane. For this reason, ingested fluoride is more rapidly absorbed in the stomach (acidic pH) than in the intestines (alkaline pH). It is the concentration gradient of non-ionic HF that is the driving force for HF transport across biomembranes.

have the same physiological distribution and potential systemic toxicity as fluoride from sodium fluoride. Therefore, studies on sodium fluoride also may be used to evaluate the potential effects of HF inhalation.

In the EPA-sponsored 90-day subchronic study (Placke and Griffin, 1991), female and male rats (20/group) were exposed to HF concentrations of 0.1, 1.0 or 10 ppm for 6 hours/day, 5 days/week. Observations included clinical signs, body weight, organ weights of liver, kidneys, testes, ovaries, adrenals, heart, spleen, brain and lungs, hematology, blood biochemistry and complete histopathology. The NOAEL in this study was 1.0 ppm. Additional information on this HF subchronic study is provided in Appendix I, p. 12.

With respect to sodium fluoride, the National Toxicology Program (NTP) has conducted repeated oral exposure studies in both rats and mice (NTP, 1990). Two-week, 6-month and 2-year studies were conducted in which sodium fluoride was administered via drinking water. The results of the 6-month study are discussed in detail in Appendix I, pp. 13-15, and are summarized here. Pathological changes of the stomach of rats were observed grossly and on histological examination. A subtle focal to diffuse hyperplasia of the mucosal epithelium of the glandular stomach was observed in most male and female rats receiving 300 ppm. Hyperplasia of the mucosal epithelium of the glandular stomach also was observed in half the males and in two females receiving 100 ppm sodium fluoride, but individual cell necrosis was not observed. No other histologically-significant pathological changes were observed in this study. In mice, compound-related effects were observed in the femur and, to a lesser extent, in the tibia of nearly all male and female mice receiving 100 to 600 ppm sodium fluoride. In mice receiving 600 ppm some lamellae appeared thicker and more irregular with cement lines that

were less prominent and smooth in contour. The osteoid seams lining some osteons (haversian canals) of the cortical bone were increased in thickness. In mice receiving 50 or 100 ppm, only occasional prominent osteoid seams were evident. Lesions of the lower incisors were generally more extensive in the mice receiving 300 or 600 ppm than in mice receiving lower doses. The apparent NOAEL for rats was 50 ppm and for mice 10 ppm.

The HF HAPs Group believes that the HF and sodium fluoride studies, considered together, provide adequate information about chronic and subchronic toxicity from HF exposures to evaluate residual risks associated with the extremely low ambient levels that can reasonably be expected to exist following installation of MACT controls.

C. Developmental Toxicity

No specific studies on the developmental toxicity of HF have been reported. However, as discussed above (Section IV.B.) and in the proposal for route-to-route extrapolation (Appendix II), the systemic toxicity of both HF and sodium fluoride are related to the generation of the fluoride ion. Therefore, developmental toxicity studies of sodium fluoride are an appropriate surrogate for HF. Oral sodium fluoride developmental toxicity studies have been reported for two species -- rats and rabbits. (Collins, *et al.*, 1995; Heindel, *et al.*, 1996.) Although these studies were not conducted via inhalation, the results reasonably can be used to predict the effects of HF exposure.

In Collins *et al.* (1995), pregnant rats were administered 0, 10, 25, 100, 175 or 250 ppm sodium fluoride in drinking water throughout gestation. No effects on reproductive outcome, and no biologically significant developmental effects were observed. Heindel *et al.* (1996) reported that pregnant rats were administered 0, 50, 150 or 300 ppm sodium fluoride in

deionized drinking water during days 6-15 of gestation. In the same study, pregnant rabbits were administered 0, 100, 200 or 400 ppm sodium fluoride in deionized drinking water during days 6-19 of gestation. No effects on reproductive outcome were observed in either species. Also, no effects on fetal body weights or developmental malformations were observed in either species. A more detailed analysis of these studies is provided in Appendix I, pp. 15-16.

In summary, these studies reveal that sodium fluoride does not induce developmental toxicity in rats or rabbits at levels up to 400 ppm in drinking water, even at levels that produced maternal toxicity. Since fluoride is the species of interest whether sodium fluoride or HF is administered, the results of these studies are sufficient to conduct residual risk determinations for HF for developmental toxicity. Thus, no additional testing for developmental toxicity is necessary for HF.

D. Reproductive Toxicity

No specific reproductive toxicity data on HF are available. As discussed above for both subchronic and developmental toxicity studies, however, the reproductive effects of sodium fluoride have been well studied. Reproductive studies with sodium fluoride reasonably can be used to assess the potential reproductive effects of HF.

The effect of sodium fluoride on fertility has been studied in mice, rats and rabbits. (Araibi *et al.*, 1989; Chinoy *et al.*, 1991; Chinoy and Sequeira, 1989; Chinoy and Narayana, 1994.) Studies have assessed the effects of fluoride on male fertility, sperm cell histology, spermatogenesis and sperm morphology. (Li *et al.* 1987; Dunipace *et al.* 1989; Sprando *et al.*, 1996.) Several two- and three-generation reproductive studies have assessed the effect of sodium fluoride on litter production, growth, reproductive response, litter size, pup

weight and incidence of stillbirth, as well as sperm count, testis weight, testicular pathology and hormonal parameters (LH, FSH or testosterone). (Messers *et al.*, 1973; Tao and Suttie, 1976; unpublished study cited in Sprando *et al.*, 1996.) Although some studies showed decreases in fertility in mice administered sodium fluoride by gavage or through the diet, other studies conducted under more rigorous conditions and at higher doses -- on a milligrams sodium fluoride per kilogram body weight basis -- indicate that fluoride is not a reproductive toxicant.

The existing studies are discussed in more detail at Appendix I, pp. 16-17. The HF HAPs Group believes that conducting additional reproduction toxicity studies with HF would not improve the quality of available information. Since high-dose, rigorous studies show that sodium fluoride, and therefore HF, is not a reproductive toxicant, no additional reproductive testing of HF is necessary.

E. Neurotoxicity

EPA has proposed neurotoxicity testing for HF using TSCA test guideline Section 799.9620. 63 Fed. Reg. at 67484. The HF HAPs Group believes that this testing is unnecessary because existing data indicate that no neurotoxic effects are likely to be detected by such testing and that no neurotoxic effects reasonably can be anticipated from HF exposures likely to occur after implementation of MACT controls.

Neurobiological studies have suggested a variety of basic mechanisms by which fluoride ion can affect the function of the nervous system. Although these studies do not specifically address the issue of neurotoxicity, they do establish the fluoride ion concentration range that is required for biological impact on the nervous system and elucidate the function of fluoride, a normal constituent of cerebrospinal fluid. Specifically, the available neurobiological

data suggests that fluoride ion can affect neuronal functions by its influence on Ca^{++} flux across neuronal membranes. (Kay *et al.*, 1986; Jope and Lally, 1988; Nakagawa-yagi, *et al.* 1993). *See* Appendix I, pp. 17-18.

Since fluoride has the ability to affect a key neurobiological process such as Ca^{++} flux, it is perhaps not surprising that relatively high exposure concentrations of sodium fluoride *in vivo* have been reported to alter behavior of rats, although such effects are quite subtle. Mullenix *et al.* (1995) studied the effects of 100 ppm of sodium fluoride in drinking water for six weeks in male and female rats.[23] The authors conducted a detailed analysis of the number of initiated behaviors, the total duration of specific behaviors, the temporal distribution -- *i.e.*, whether behaviors were clustered or dispersed in time -- of specific behaviors, and the temporal distribution for sequences of different types of behavior. The analysis involved over 100 dependent variables for each rat for each category of initiations, duration, and temporal distribution. Whereas the male rats were not affected, females showed several statistically significant differences relative to control with respect to initiations of sitting behavior, grooming-attention sequences, and grooming-exploration sequences. These subtle changes are not considered neurotoxic effects because they do not diminish the organism's ability to adapt to a changing environment. With respect to the vast majority of the hundreds of other measures -- including parameters measured under EPA's test guidelines -- the authors reported no significant effect in the treated animals.

The HF HAPs Group regards the conduct of a guideline neurotoxicity test battery as unnecessary, because the findings of the Mullenix study -- as well as other relevant animal

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23 The amount of sodium fluoride that can be repeatedly administered is limited by the incidence of death associated with dehydration that occurs at about 175 ppm in drinking water.

data -- demonstrate the absence of clinical signs of neurotoxicity, including the absence of pathological effects on brain tissue in several standard toxicology studies. Protocols conducted under applicable EPA neurotoxicology test guidelines can detect gross phenomena such as tremors and ataxia or substantial (30-40%) increases and decreases in the amount of motor activity, and such effects were not observed in the Mullenix study. The behavioral effects that were observed in the Mullenix study are too subtle to be among the kinds of effects that could be detected by EPA's guideline neurotoxicity test. It is furthermore unlikely that the neuropathological evaluation conducted under guideline tests would reveal any structural anomalies that were not detected in existing subchronic toxicology studies which included microscopic evaluation of brain tissue by standard pathological methods. (Placke and Griffin, 1991; NTP, 1990.) Thus, existing data indicate that the neurotoxicity testing proposed by EPA would not detect any neurotoxicity effects from hydrogen fluoride exposure.

In its June 26 Response, EPA pointed out that there have been no systematic studies comparing the Mullenix method with the standard neurotoxicity battery. The HF HAPs Group believes, however, that review of the methodology of Mullenix is sufficient to show that it measured more complex behavior -- and therefore observed more subtle effects -- than would be possible under the standard neurotoxicity battery. EPA should not reject the results of Mullenix *et al.* simply because that study did not conform to its latest test guidelines -- rather, the issue is whether additional testing is needed to adequately characterize the neurotoxicity potential of hydrogen fluoride.

The HF HAPs Group notes that a very large number of people have been exposed to fluoride on a daily basis over a very long period of time, through drinking water and certain

consumer products such as toothpaste and mouthwash. To the best of the HF HAPs Group's knowledge, there are no reports of an adverse effect on the structure or function of nervous system associated with these fluoride exposures. Based on this lack of observed neurotoxic effects in humans and the results of animal studies, including the Mullenix *et al.* study, the HF HAPs Group believes that no neurotoxic effects reasonably can be anticipated from the extremely low HF exposures that are likely to occur after implementation of MACT controls.

Accordingly, conducting EPA guideline neurotoxicology tests is not necessary, because such studies would not increase the ability of EPA to identify and assess any risk that might be associated with exposure to fluoride. The proposed neurotoxicology studies should be eliminated because such studies would not improve the quality of information that already is available.

F. Immunotoxicity

EPA proposes immunological testing of HF using TSCA test guideline Section 799.780. The HF HAPs Group believes that such testing is not necessary. Although no studies have specifically evaluated the immunotoxicity of inorganic fluorides, data from repeated dose HF and inorganic fluorides studies, as well as epidemiological studies of communities with fluoridated water supplies, indicate that fluorides do not produce immunotoxic effects.

In an EPA-sponsored inhalation study, rats were exposed to HF at 0, 0.1, 1.0 or 10 ppm for 90 days. (Placke and Griffin, 1991.) No histopathological effects were reported in the spleen, thymus or bone marrow. Slight changes in several hematological parameters (*e.g.*, decreased lymphocytes, increased white blood cell counts) were observed -- the study authors

judged these changes to have minimal toxicological significance, and these effects were probably secondary to the decreased food consumption and the dental malocclusion noted in the animals.

Numerous epidemiology studies have been conducted in communities with fluoridated water supplies with no evidence of immunosuppression or increased sensitivity to infection or other disease associated with fluoride exposures. In addition, the American Academy of Allergy concluded that no suggestions of any immune reactions occurred with oral exposure to fluoride. (ATSDR, 1993).

At least four chronic bioassays have been conducted with sodium fluoride. Mice were exposed to sodium fluoride in their drinking water for two years to 25, 100 or 175 ppm (NTP, 1990), or in their feed to 4, 10 and 25 mg/kg/day (Maurer, *et al.* 1993). Hematological and histopathological examinations did not suggest any immunological involvement. A similar lack of immunological involvement was noted in two chronic rat studies with dose levels up to 4.29 mg F/kg/day in a drinking water study (NTP, 1990), and up to 11.24 mg F/kg/day in a feeding study (Maurer, *et al.* 1990). In the NTP rat and mouse drinking water studies, histopathological evaluations included mandibular and mesenteric lymph nodes, bone marrow, spleen and thymus at 24 and 66 weeks, and at study termination at 105 weeks. Hematology measures, performed at 24 and 66 weeks in rats and at 24 and 66 weeks in mice, included white blood cell count with differentials and platelet counts. No toxicologically significant findings were observed in these studies, and there was no effect on survival.

There are two major consequences associated with immunosuppression in animals or man. The most common is an increased susceptibility to infections by bacteria, viruses, fungi and parasites. A frequent complication is an increased incidence of cancer. Numerous

epidemiology studies (reviewed in ATSDR, 1993) have examined the relationship between fluoridated water and cancer. The weight of evidence strongly suggests that no relationship exists between fluoride exposure and cancer incidence. One of the most recent and thorough studies examined more than 2,300,000 cancer deaths and more than 125,000 cancer cases in U.S. counties exposed to artificially fluoridated drinking water for up to 35 years. (Hoover, *et al.*, 1991, as cited in ATSDR, 1993.) No relationship between cancer incidence or mortality and duration of fluoridation was found. In addition, one study reported an inverse relationship between fluoride levels and cancer of the oral cavity and pharynx for populations in Norway. (ATSDR, 1993.)

In conclusion, data from numerous epidemiology studies of populations exposed to fluoridated drinking water, extensive histopathological and hematological examinations from four lifetime dosing studies with sodium fluoride in rats and mice, and a 90-day inhalation study with HF in rats do not show an association with increased susceptibility to infection, increased mortality or carcinogenicity. The available evidence therefore provides no evidence that fluorides are immunotoxic, and additional testing for this parameter is not necessary.

G. An Iterative Approach to Testing Is Particularly Appropriate for HF

For the reasons described above, the HF HAPs Group does not believe that any additional testing is necessary to characterize the risks from potential exposure to HF. If EPA proceeds to a final test rule, however, the HF HAPs Group believes that, at a minimum, EPA should adopt an iterative approach to testing, rather than automatically requiring "Option Three" testing for HF. This issue, as it pertains to all chemicals, is discussed further in CMA's separate comments on general issues. Under an iterative approach as recommended by the National

Academy of Sciences, HAPs would be prioritized based on their acute toxicity and chemical structure. As necessary, acute toxicity testing, followed by data on uptake, distribution, retention and excretion of the compound, followed by subchronic toxicity testing, would be a more logical and cost-effective approach. Testing for specific endpoints would then be required as necessary based on the results of subchronic tests. 61 Fed. Reg. at 33183.

The HF HAPs Group has submitted an alternative testing proposal for HF that takes an iterative approach to testing (*see* Appendix II). This approach recommends inhalation studies to examine portal of entry effects, followed by studies that allow route-to-route extrapolation for HF and sodium fluoride. Data from these proposed studies, in conjunction with existing data, would suffice for any residual risk analysis.

An iterative approach such as this is desirable because it ensures that a database is developed that characterizes the health effects of the chemicals sufficiently to allow EPA to conduct residual risk analyses, while at the same time only expending those resources that are needed to develop an adequate understanding of the chemical's toxicity at reasonably anticipated exposure scenarios. Thus, the approach conserves resources and laboratory capacity and ensures that laboratory animals are not sacrificed needlessly. Such an iterative approach likely would show that EPA's proposed testing is not necessary to characterize risks from HF.

EPA states that it has declined to adopt an iterative approach because: (1) it claims to have prioritized chemicals based on consideration of exposure potential; (2) iterative testing based on toxicity would be time-consuming and require multiple rulemakings, taking too long to be useful for meeting statutory deadlines under the CAA; (3) iterative testing would be "prohibitively costly to EPA and would not recognize the limitations on EPA resources"; and (4)

the "multichemical decisions required under Section 112 of the CAA . . . [require] a consistent, even database covering HAPs across the same broad set of endpoints." 61 Fed. Reg. at 33183.

As described by CMA in its comments, however, the advantages of the iterative approach outweigh the disadvantages identified by EPA because: (1) although EPA claims to have prioritized chemicals based on "exposure potential," the Agency instead prioritized chemicals based on releases; (2) an iterative approach would not necessarily be more time-consuming or require multiple rulemakings because initial testing may generate sufficient information for residual risk assessments, making further testing unnecessary; (3) the approach adopted by EPA may consume Agency resources unnecessarily, as Agency scientists will be required to analyze large amounts of technical data that, in the end, may have no relevance or only marginal relevance to EPA's regulatory activities; (4) attempting to test too much for the first group of 189 HAPs will hold back the residual risk program as a whole and may lead to arbitrarily inconsistent treatment of various HAPs; and (5) EPA has not presented an adequate justification for why it needs a uniform data set for all chemicals before it can conduct the necessary analyses under the Clean Air Act. In fact, the *Draft Residual Risk Report to Congress* states that EPA will use a prioritization scheme for selecting which risk value to use for a chemical, thus indicating that a uniform data set is not necessary. Therefore, the HF HAPs Group urges EPA to apply an iterative approach to any testing required for HF under TSCA Section 4.

V. EPA HAS NOT ADEQUATELY JUSTIFIED ITS FINDINGS UNDER TSCA SECTION 4 IN SUPPORT OF ITS PROPOSED TESTING REQUIREMENTS FOR HYDROGEN FLUORIDE

A. EPA Has Not Shown That Existing Data Are "Insufficient" To Predict The Effects Of Hydrogen Fluoride On Human Health And The Environment

Under TSCA Section 4, EPA must find that there are "insufficient data and experience" to determine or predict the effects of the chemical on human health and the environment. TSCA § 4(a)(1)(A)(ii), § 4(a)(1)(B)(ii). This analysis, however, cannot be conducted in a vacuum. Because information is never complete, and because less recent studies always can be shown to be less than ideal when compared against new testing guidelines, existing data always are imperfect in some sense. This is true even where the existing data clearly demonstrate the presence or absence of an effect on human health or the environment, and even where existing data cover virtually all endpoints.

Thus, in drafting TSCA Section 4, Congress recognized that, while infinite quantities of data are desirable in a perfect world, in a world of limited resources the data gathered should be tied closely to the regulatory purposes for which they are used. For the findings required by TSCA Section 4 to have meaning, therefore, they must be tied to the basis for the testing. That is, EPA must show why the existing data are insufficient for the regulatory purposes for which they are to be used.

Here, EPA has stated expressly that the data are needed to conduct residual risk analyses.[24] Yet nowhere in its findings has EPA made a showing that the existing data for HF are insufficient to conduct residual risk analyses. Instead, EPA has identified perceived inadequacies of certain portions of the database, but has not shown that those asserted

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24 61 Fed. Reg. at 33179; EPA June 26 Response at 2.

deficiencies render the overall database inadequate to perform residual risk assessments under the Clean Air Act. Moreover, by refusing to consider likely levels of exposure, EPA fails even to attempt to conduct the statutorily-required analysis. As a result, EPA's proposal does not meet the requirements of TSCA Section 4.[25]

Specifically in the case of HF, the HF HAPs Group believes the existing data are sufficient to conduct residual risk determinations. As described above, numerous acute studies have been conducted on HF, adequately characterizing its acute toxicity. Indeed, these data already have been used to recommend AEGLs for HF. Although few subchronic HF studies exist, the fluoride ion is responsible for any systemic toxicity from HF, and sodium fluoride has been tested extensively both in animal and epidemiological studies. These existing data are sufficient to characterize the toxicity of HF for all endpoints for which testing has been proposed. EPA has made no showing as to why this extensive database is "inadequate" to enable EPA to make residual risk determinations and otherwise fulfill its obligations under the Clean Air Act.

B. EPA Has Not Demonstrated That The Proposed Testing For Hydrogen Fluoride Is "Necessary" To Support EPA's Risk Management And Risk Assessment Functions

Under TSCA Section 4, EPA must also make a finding that the testing proposed to be required is "necessary" to develop "such data," *i.e.*, to develop the data necessary to predict the effects of the chemical on human health or the environment. TSCA §§ 4(a)(1)(A)(iii) and (B)(iii). It is important to remember, however, that the purpose of TSCA is not to create a perfect database for every chemical. Rather, the purpose of TSCA is to regulate chemicals and chemical substances to prevent "unreasonable risk[s] of injury to human health and the

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25 Such a requirement is an obvious corollary to Congress' explicit recognition in TSCA of the need to balance environmental concerns against economic feasibility. *See* below at note 26.

environment." TSCA § 2(a)(2). To that end, the statute states that it is the "policy" of TSCA to ensure that "adequate data [are] developed with respect to the effect of chemical substances and mixtures on health and the environment." TSCA § 2(b)(1) (emphasis added).[26]

To accomplish these purposes in the testing context, EPA must show that the testing it proposes to require is necessary not to provide a complete data set, but rather, to provide "adequate data" to conduct residual risk determinations.[27] For the reasons discussed above, such a finding cannot be made for HF. Indeed, by establishing AEGLs for accidental releases, EPA already has achieved the outcome for which it now proposes acute toxicity testing (*i.e.*, a risk determination). As discussed above, the HF HAPs Group believes that available subchronic and chronic information is likewise sufficient to conduct residual risk determinations for HF.

EPA did not attempt to conduct the requisite analysis to show that its proposed testing meets the "necessity" requirement of TSCA Section 4. Instead, EPA merely stated that the proposed testing "is necessary to develop data" for the endpoints specified in the rule, and that this testing is needed generally to "determine if the manufacturing, processing, and use of hydrogen fluoride does or does not present an unreasonable risk of injury to human health from inhalation exposure." TSCA Section 4 Findings at 52. EPA's conclusory statements cannot be considered a finding that each test proposed for HF is "necessary" to enable EPA to meet the

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26 Consistent with TSCA's goal of balancing the need to protect human health and the environment with economic feasibility, the statute further provides that any actions taken under TSCA should include consideration of the "environmental, economic and social impact" of those actions, and any authority should be exercised so as "not to impact unduly or create unnecessary economic barriers." TSCA §§ 2(c) and (b)(3).

27 This interpretation is consistent with the House Committee Report, which specified that EPA must "eliminate unnecessary or duplicative testing." H.R. Rep. No. 1341 at 18.

requirements of the Clean Air Act. The Agency does not even attempt to connect the required testing to the purposes for which the data will be used. For example, there is no explanation in the rulemaking record of why EPA believes the proposed immunotoxicity testing is necessary to provide "adequate data" to enable EPA to conduct a residual risk determination for HF. Because EPA has failed to make the findings required by the statute, the Agency has failed adequately to support its proposed test rule.

C. EPA's "A" Finding For HF Is Not Adequately Justified

EPA purports to make a finding that the manufacture, processing, distribution, use or disposal of HF may present an unreasonable risk of injury to health, as required under TSCA Section 4(a)(1)(A) (the "A" finding). 61 Fed. Reg. at 33192. EPA bases its claim on eye irritation and other effects from acute exposures, as well as respiratory and liver toxicity observed in some repeated dose studies. TSCA Section 4 Findings at 47. EPA has not supported adequately its purported "A" finding that HF may present an unreasonable risk of injury to human health. As explained further below, EPA has not complied with the requirement that it correlate HF's suspected toxicity with anticipated levels of exposure. EPA also has improperly used its "A" findings for three endpoints to require testing for other, unrelated endpoints.

First, EPA has not attempted to correlate suspected toxicity with suspected exposure levels. However, a determination under Section 4(a)(1)(A) that a chemical "may present" an unreasonable risk depends on an analysis of human exposure to the substance and its potential toxicity. *See Chemical Manufacturers Association v. EPA*, 859 F.2d 977, 983 (D.C. Cir. 1988) ("the *EHA*[28] decision"). After reviewing the legislative history of TSCA, the court

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28 2-Ethylhexanoic acid.

found that "Congress obviously intended Section 4 to empower EPA to issue a test rule only after it had found a solid 'basis for concern' by accumulating enough information to demonstrate a more-than-theoretical basis for suspecting that an 'unreasonable risk' was involved in the use of the chemical." 859 F.2d at 986. Thus, the court held, "[t]he statutory standard requires EPA to correlate the suspected toxicity of a substance with the suspected levels of exposure." *Id.* at 995 (emphasis added). Demonstrating such a relationship is a minimum requirement for a "may present" finding. According to the court, a Section 4 test rule "is warranted when there is a more-than-theoretical basis for suspecting that some amount of exposure occurs and that the substance is sufficiently toxic at that exposure level to present an 'unreasonable risk of injury to health.'" *Id.* (emphasis added).[29] EPA's testing proposal discusses each of these factors (exposure and toxicity) separately, but does not discuss them together, and does not provide sufficient information to determine the basis for EPA's finding of potential unreasonable risk for HF.

Specifically, EPA has failed to relate the HF exposure scenarios to its toxicological concerns, as required by the *EHA* decision. EPA has not explained why the endpoints for which testing is proposed are of concern in light of the reasonably anticipated duration, level and scope of human exposure to HF.[30] To fill this gap, EPA must expand its analysis of exposure and release scenarios and relate them to the specific toxicity concerns underlying its testing proposal for HF. Without this additional analysis, adequate support will be

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29 The mere fact that there has been a release does not necessarily mean that there has been any exposure. For example, substances may be rapidly dispersed, degraded or reacted such that even relatively large releases do not necessarily result in exposures.

30 As discussed at Section V.D.3., below, potential worker exposures are not properly a basis for this test rule, which is intended to develop information to conduct residual risk determinations under the Clean Air Act.

lacking for a finding under TSCA Section 4(a)(1)(A) that HF "may present" an unreasonable risk of injury to human health.

The HF HAPs Group believes that such an analysis in fact would demonstrate that HF is not likely to pose an unreasonable risk of injury to human health at reasonably expected exposures to ambient HF. The toxicity of HF is well understood and stringent controls and guidance accordingly have been developed to prevent and mitigate releases of hydrogen fluoride.[31] For example: the American Petroleum Institute (API) issued in 1992 its Recommended Practice 751, *Safe Operation of Hydrofluoric Acid Alkylation Units*; the Hydrogen Fluoride Industry Practices Institute provides guidance on the safe handling of HF and has several task groups to address various aspects of safe handling of HF; and the Occupational Safety and Health Administration (OSHA) requires a process safety management system for any process involving anhydrous HF at 1000 pounds or more. 29 C.F.R. § 1910.119. In addition, as discussed below in Section V.D.2., potential exposures to HF will decrease greatly as MACT controls are implemented. Thus, both acute and chronic levels of HF are likely to be low. The HF HAPs Group believes that a comparison of the likely levels of ambient HF to the effect levels in existing studies would indicate that HF is not likely to pose an unreasonable risk of injury to human health.

Second, EPA improperly seeks to escape its obligation to correlate the suspected toxicity of HF with the suspected level of exposure by claiming that, once it has made an "A" finding for any toxicological endpoint, "EPA may require any type of health or environmental effects testing necessary to address unanswered questions about the effects of the chemical

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31 EPA (1993). *Hydrogen Fluoride Study Final Report: Report to Congress, Section 112(n)(6), Clean Air Act As Amended* (EPA 550-R-93-001) [Hydrogen Fluoride Study].

substance" -- whether or not those tests are in any way related to the health effect endpoint for which the "A" finding was made. TSCA Section 4 Findings at 3. Indeed, though the "A" findings for hydrogen fluoride are based on respiratory toxicity, liver toxicity and eye irritation, EPA proposes to require testing for several unrelated endpoints, including developmental toxicity, reproductive toxicity, neurotoxicity and immunotoxicity.

EPA's approach is inconsistent with the language and intent of TSCA Section 4, and represents misguided policy. It is clear that Congress did not intend an "A" finding under TSCA Section 4 for one endpoint to give EPA *carte blanche* to require any kind of testing it may desire. For this statutory language to have any meaning at all, the testing to be required by EPA must be tied to the health effects endpoints which are of legitimate concern, *i.e.*, those that "may present an unreasonable risk" at levels likely to exist after implementation of MACT controls. EPA's contention that an "A" finding for one endpoint gives the Agency unrestricted license to address all "unanswered questions about the effects of the chemical substance" disregards the clear intent of Congress to strike a balance between the Agency's legitimate information needs and the obvious reality that the number of chemicals in commerce is great and testing resources are limited.[32]

D. EPA's "B" Finding Is Not Warranted For HF

In it comments, CMA explains why the numeric criteria used to make EPA's "B" findings do not provide a meaningful basis for determining whether exposure is sufficient to

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32 EPA's failure to make meaningful findings concerning the "necessity" of testing for each endpoint or the "necessity" of each study for each of the compounds makes it all the more critical that the Agency develop appropriate and well-supported "A" and "B" findings.

warrant testing. The HF HAPs Group incorporates CMA's comments by reference. In addition, a few points warrant mention specifically with regard to HF.

1. Before Requiring Testing, EPA Should Evaluate General Population Exposures to HF

In a previous proposed test rule for aryl phosphate base stocks, EPA acknowledged that it should require testing only where "human or environmental exposure is of such magnitude or type that [the chemical] may need to be regulated if test data reveal adverse effects." 57 Fed. Reg. 2138, 2144 (Jan. 17, 1992) (emphasis added). In the current rulemaking, however, EPA did not consider the realistic potential for human exposure to HF. This omission is critical because the Agency's primary justification for requiring testing is to develop data to support EPA's residual risk determinations under the Clean Air Act.[33] Yet EPA has not attempted to determine current general population exposures from industrial releases of HF, or, more significantly, what those exposures are likely to be after implementation of MACT standards.[34] EPA also failed to consider that HF already is highly regulated and handled at facilities with extreme care. Without an exposure analysis, EPA cannot determine whether its proposed testing is justified from a legal, practical, or policy perspective.

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33 *See* Part III, above.

34 EPA's Exposure Profile for HF (Docket Number B1-283, pp. 104-107) does no more than speculate that "residents downwind from effluent stacks may be exposed to hydrogen fluoride in air" and that "[p]eople living in homes or areas where homes are heated with coal may be exposed to hydrogen fluoride in the air." The only air concentration of HF mentioned in the Exposure Profile is a level of 0.2-0.3 mg/m^3 measured at a German incinerator. EPA made no attempt to estimate likely air concentrations of HF from current releases of HF in the U.S., much less from releases that will occur after implementation of MACT.

2. TRI Data Do Not Provide A Reasonable Measure of Potential Exposure

EPA selected chemicals for the initial HAP test rule based on the volume of emissions reported to the TRI. The proposal states that EPA selected HAPs "for initial consideration by focusing its attention on HAPs with TRI emissions of 50 tons or more per year." 61 Fed. Reg. at 33184. However, EPA's Science Advisory Board has expressly recognized that TRI data on emissions do not provide a good measure of actual exposure:

> The TRI emissions data . . . do not reflect toxicity/potency of various pollutant emissions and are not related to exposure in a simple way, *i.e.*, large emissions do not automatically imply large exposures and risks.[35]

Thus, although the Agency proposed testing only for compounds with aggregate air emissions in excess of 50 tons per year, this does not provide a measure of potential exposure because EPA did not attempt to evaluate quantitatively or qualitatively the nature or pattern of the releases to air, or the potential for significant general population exposure from the releases.

Moreover, HF emissions likely will decline significantly over the next several years, as facilities comply with MACT standards. On October 7, 1997, EPA published the final MACT standards for Primary Aluminum Reduction Plants, which specifically target HF emissions. 62 Fed. Reg. at 52384. EPA estimates that the rule will reduce fluoride emissions from current levels by 50 percent. *Id.* at 52391. EPA is scheduled to promulgate MACT standards by the year 2000 for the Hydrogen Fluoride Production, Phosphate Fertilizer

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35 Letter to Carol M. Browner, EPA, from Dr. Genevieve Matanoski, Dr. Mark Harwell and Dr. Rolf Hartung, Science Advisory Board, regarding "Science Advisory Board Review of the Technical Basis for Listing Ammonia on the Toxics Release Inventory" (Feb. 2, 1995). The letter further stated that Science Advisory Board members "expressed concerns about the potential for misinterpretation of the TRI data and for inadvertently directing environmental protection efforts away from the areas of most significant risk." *Id.*

Production, Phosphoric Acid Production, and Uranium Hexafluoride Production sources categories.[36] EPA has identified HF as the major HAP emission of concern for each of these categories.[37] In addition, EPA plans to control HF under the Petroleum Refinery Catalytic Cracking MACT standard, scheduled for final promulgation in 1999.[38] The 1993 TRI data relied upon by EPA for its release estimates obviously do not reflect any reduction in emissions resulting from compliance with MACT standards. Nor does EPA's testing proposal in any other way address these anticipated reductions in emissions.

In addition to MACT standard controls, facilities that produce or process HF have implemented process safety management systems and other practices to minimize the potential for HF releases and to mitigate any releases that do occur. These practices are described in Chapters 6 and 7 of EPA's Hydrogen Fluoride Study.[39] They include use of special equipment to prevent leakage from valves and flanges, monitoring systems to detect leaks, and scrubbers or water spray systems to prevent dispersion of released HF.

Furthermore, any HF emissions that do reach the fence line are not likely to persist in the atmosphere. HF rapidly reacts with water in the atmosphere and is quickly washed

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36 61 Fed. Reg. 28197, 28205-06 (June 4, 1996). Currently, EPA plans to publish final standards in 1998 for Phosphate Fertilizer and Phosphoric Acid Production, in 1999 for Hydrogen Fluoride Production, and in 2000 for Uranium Hexafluoride Production. <http://www.epa.gov/ttn/uatw/7_10yrstds.html> (updated May 11, 1998).

37 *See* EPA (1992). *Documentation for Developing the Initial Source Category List.* 3-13 to 3-14 (EPA-450/3-91-030).

38 *Id.* at 3-7. EPA originally scheduled the Petroleum Refinery Catalytic Cracking Standard for promulgation in 1997. 61 Fed. Reg. at 28203. EPA now plans to issue the proposed standard in June 1998 and the final standard in July 1999. <http://www.epa.gov/ttn/uatw/ 7_10yrstds.html> (updated May 11, 1998).

39 *See also* note 31 above, and accompanying text.

out. Once in contact with soil, the HF solution reacts to form fluoride salts, so that no revolatilization of HF is likely.

3. EPA Should Not Base Its "B" Finding On Worker Exposure

EPA's "B" finding is based in part on worker exposure. *See* TSCA Section 4 Findings at 48. Worker exposures, however, are unrelated to the purpose for which the testing is being required. The proposed test rule is first and foremost a HAP test rule; it is intended to generate data for evaluating residual risks, after the installation of MACT standards, of air emissions to the general population.[40] Accordingly, EPA's statements about potential worker exposures simply are not relevant to support the proposed HAP test rule.

Even if worker exposure were relevant, EPA has used outdated data in its findings. EPA cites a 1989 NIOSH survey (which merely estimated potential worker exposure), a 1990 article concerning HF concentrations in a single department of a single company, a 1982 study of HF concentrations in a single chrome plating shop, and a study estimating HF concentrations at an oil refinery from 1961-1971. TSCA Section 4 Findings at 48. EPA did not consider the impact of changes in technology nor of process controls, such as OSHA's 1992 process safety management rule (29 C.F.R. § 1910.119), on the potential for worker exposure.

Furthermore, even if potential worker exposure is "substantial," it does not follow that there are "insufficient data and experience" concerning the potential effects of HF in the workplace. *See* TSCA § 4(a)(1)(B)(ii). In fact, the existing data and experience on HF have been sufficient to lead to development of an OSHA permissible exposure limit (29 C.F.R.

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40 61 Fed. Reg. at 33179; EPA June 26 Response at 2.

§ 1910.1000, Table Z-2), an OSHA process safety management standard (29 C.F.R. § 1910.119), and industry guidelines and practices for worker protection.[41]

First and foremost, however, the issue for the HAP test rule is whether additional testing of HF is necessary for EPA to conduct its residual risk analyses under the Clean Air Act, not whether there is potential worker exposure. For the reasons given above, the HF HAPs Group believes that EPA has not made such a showing.

CONCLUSION

For the reasons described above, the HF HAPs Group believes that additional testing of HF is not necessary to support residual risk analyses under the Clean Air Act. Moreover, the HF HAPs Group believes that EPA has not adequately supported the findings required to support testing under TSCA Section 4. Accordingly, the HF HAPs Group believes that if any testing is to be conducted on HF as part of this testing initiative, it should consist only of the testing identified in the HF HAPs Group's Alternative Testing Proposal. The HF HAPs Group appreciates the opportunity to submit comments on EPA's testing proposal, and reiterates its support for the steps taken by EPA to support a constructive dialogue on issues presented by EPA's testing proposals.

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41 Hydrogen Fluoride Study, Chapters 6-7. *See* notes 31 and 39, above, and accompanying text.

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APPENDIX I

SUMMARY OF HYDROGEN FLUORIDE TOXICITY DATA

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JUNE 22, 1998

I. *Acute Inhalation*

EPA proposes to use the Acute Inhalation Toxicity with Histopathology Test Guideline (40 C.F.R. § 799.9135) to study the acute sublethal effects of HF, especially effects on the respiratory system associated with accidental release and acute exposures. The goals of this test are to characterize the exposure-response relationship following acute exposure. This guideline is designed primarily to assess two endpoints: (1) histopathology of the respiratory tract, kidney, liver, and other target organs; and (2) cell damage via lung lavage.

The HF Panel believes that existing acute inhalation data for HF sufficiently characterize an exposure-response relationship for sensitive endpoints (blood analyses, bronchoalveolar lavage fluid analyses to evaluate cytological and biochemical parameters, pulmonary function tests, organ weight measurements, and histopathological examination of the respiratory tract and other major organs) following acute exposure to HF. Additionally, acute inhalation studies in several animal species adequately characterize the toxicological responses (lethal and sublethal) to acute high exposures to HF relative to spills and other accidental releases. Some studies demonstrate evidence of regional deposition of inhaled HF at sites of contact, while other studies include histopathological examination to evaluate regeneration or repair of affected tissues after inhalation exposure to HF. Acute inhalation data with humans are limited, but studies exist which have been useful for recommending current acute exposure guideline levels.

A. Animal Studies

Stonybrook Laboratories (1996) recently completed an acute inhalation study to assess concentration responses of nonlethal exposures to HF over a range of times normally expected for most accidental releases to occur, 10 minutes or less. A mouth-breathing model (using intratracheally-cannulated Sprague-Dawley rats) was used to deliver HF directly to the trachea in the lower respiratory tract, avoiding deposition of HF in the nose. This exposure method was considered a conservative approach and was intended to simulate a "worst-case" exposure in which a person would not breath through the nose and would inhale liberally through the mouth, thus maximizing the deposition of HF in the lower respiratory tract.

As presented in Table 1, 2- and 10-minute exposures to HF in the mouth-breathing rat model produced definite dose-response relationships for several sensitive endpoints (*e.g.*, blood enzyme activity, lung inflammation and cell damage, pulmonary function, wet and dry lung weights, and histopathological findings in the respiratory tract). In a separate group of mouth-breathing rats, respiratory lesions produced by a 10-minute acute exposure to 1454 ppm HF were repaired 3 weeks after exposure. The endpoints evaluated were mortality, blood changes, pulmonary function, organ weight changes, and histological changes. The

Table 1: Effects of 2- and 10-Minute Exposures to HF in the Mouth-Breathing Rat Model[1]

Approximate C x t	Endpoint	2-Minute Exposure	10-Minute Exposure
70000		not tested	7014 ppm
	mortality		80% mortality
38500		not tested	3847 ppm
	mortality		50% mortality
17000		8621 ppm	1764 ppm
	mortality	5%	5%
	blood anal.	↑ AST, ALT, SDH, RBC, Hb, Hct	↑ SDH, Hb, Hct
	BALF anal.	↑ TP, MPO, LDH, G-6-PDH, β-gluc., PMNs, sialic acid	↑ TP, MPO, LDH, β-gluc, PMNs, sialic acid
	pul. funct.	↓ TLC, VC, ↑ RV, ↓ flows FEV, ↑ Rpul, ↓ Dlco	↓ flows FEV, marginal ↓ Dlco
	organ wts.	↓ spleen & thymus wt, ↑ wet & dry lung wt	↑ wet lung wt
	histology	tracheal inflammation, exudate & necrosis-, bronchial exudate & necrosis; alveolitis	tracheal inflammation, exudate & necrosis-, bronchial necrosis
9500		4887 ppm	950 ppm
	mortality	10%	none
	blood anal.	↑ SDH	↑ AST
	BALF anal.	↑ TP, MPO, LDH, ß-gluc., PMNs, sialic acid	↑ PMNs, MPO
	pul. funct.	↑ RV, ↓ flows FEV, ↑ Rpul	marginal ↓ flow at 25% FVC
	organ wts.	↑ wet & dry lung wt	none
	histology	tracheal inflammation, exudate & necrosis-, bronchial exudate & necrosis; alveolitis	tracheal inflammation, exudate & necrosis
2800		1589 ppm	271 ppm
	mortality	none	none
	blood anal.	↑ AST	none
	BALF anal.	↑ TP, MPO, LDH, ß -gluc.	none
	pul. funct.	↓ flows at 25% FVC, ↑ Rpul	none
	organ wts.	none	none
	histology	tracheal inflammation, exudate & necrosis	tracheal inflammation
1200		593 ppm	135 ppm
	mortality	none	none
	blood anal.	none	none
	BALF anal.	none	none
	pul. funct.	none	none
	organ wts.	none	none
	histology	none	none

[1]AST = aspartate aminotransferase; ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase; RBC = red blood cells; Hb = hemoglobin; Hct = hematocrit; BALF = bronchoalveolar lavage fluid; TP = total protein; MPO = myeloperoxidase; LDH = lactate dehydrogenase; G-6-PDH = glucose-6-phosphate dehydrogenase; β-gluc. = β-glucose; PMNs = polymorphonuclear leukocytes; TLC = total lung capacity; VC = vital capacity; RV = residual volume (lung volume at end of forced exhalation); FEV = forced expiratory volume maneuver (max. forced exhalation); Rpul = pulmonary resistance; Dlco = single-breath carbon monoxide diffusing capacity

effects of HF on recovery group rats were compared to those of mouth-breathing rats which were sacrificed one day after exposure to 950 and 1764 ppm HF for 10 minutes. Results showed no mortality, no blood changes, no pulmonary function changes, and no lower respiratory tract lesions in recovery group animals examined 3 weeks after exposure to 1454 ppm HF for 10 minutes. In comparison, a number of toxic effects (refer to Table 1) were noted in rats examined one day after exposure to either 950 or 1764 ppm HF for 10 minutes.

Data shown in Table 2, compared to data in Table 1, show that the mouth-breathing rat model used in this study was more sensitive than the rat nose-breathing model. Exposure to 6392 ppm HF for 2 minutes or 1669 ppm HF for 10 minutes caused toxic effects limited generally to the nose of normal nose-breathing rats; no deaths occurred. Furthermore, no mortality occurred in normal nose-breathing rats exposed to 3847 and 7014 ppm HF for 10 minutes. In comparison, Table 1 shows serious lung effects and a low incidence of mortality in mouth-breathing rats exposed to 4887 and 8621 ppm HF for 2 minutes, and to 1764 ppm HF for 10 minutes (Table 1). Additionally, mouth-breathing rats exposed to 3847 and 7014 ppm HF for 10 minutes produced 50% and 80% mortality, respectively.

Table 2: Effects of 2- and 10-Minute Exposures to HF in Normal Nose-Breathing Rats[1]

Approximate C x t	Endpoint	2-Minute Exposure	10-Minute Exposure
70000		not tested	7014 ppm
	mortality		none
38500		not tested	3847 ppm
	mortality		none
17000		not tested	1669 ppm
	mortality		none
	clinical signs		rales & nasal discharge
	blood anal.		↑ RBC
	BALF anal.		none
	pul. func.		↑ nasal resistance
	organ wts.		none
	histology		necrosis & hemorrhage in nose
12800		6392 ppm	
	mortality	none	
	clinical signs	rales & nasal discharge	
	blood anal.	↑ RBC	
	BALF anal.	none	
	pul. func.	↑ nasal resistance	
	organ wts.	none	
	histology	necrosis & hemorrhage in nose	

[1]See footnote to Table 1 for abbreviations

Table 3: Effects of 60-Minute Exposures to HF in the Mouth-Breathing Rat Model[1]

Approximate C x t	Endpoint	60-Minute Exposure
2800		48 ppm (equivalent to ERPG-3)
	mortality	none
	blood anal.	none
	BALF anal.	↑ TP
	pul. func.	↑ lung volume
	organ wts.	none
	histology	none
1200		20 ppm (equivalent to ERPG-2)
	mortality	none
	blood anal.	none
	BALF anal.	none
	pul. func.	none
	organ wts.	none
	histology	none

[1]See footnote to Table 1 for abbreviations

Results of the Stonybrook Laboratory (1996) study also support the American Industrial Hygiene Association's (AIHA's) published ERPG-2 and -3 values of 20 and 50 ppm HF, respectively. (AIHA, 1991.) Table 3 shows that a 60 minute exposure to 20 ppm HF did not cause any toxic effects in mouth-breathing rats when evaluated one day later. The same table shows that a 60-minute exposure to 48 ppm HF produced minor signs of irritation in the airways, exudation of serum accompanied by an alteration of pulmonary function, when evaluated one day later.

Results from an acute inhalation study with HF demonstrated a concentration-response in rats at low (43% RH) and high (76%) humidity (DuPont 1990). Groups of four male Crl:CD®BR rats were exposed head-only to HF for one hour at concentrations ranging from 950 to 2730 ppm. Results showed that the 1-hour LC_{50} value of 2240 at low (43%) relative humidity was not significantly different from the 1-hour LC_{50} value of 2340 ppm at high (76%) relative humidity. In addition to mortality data, the respiratory tract histopathology was evaluated 1 and 14 days after administration of a nonlethal concentration (~ 1800 ppm HF). Tissues from the nose, larynx/pharynx, trachea and lung were examined. Pathological injury was limited exclusively to the anterior section of the nose 1 day after exposure. Histopathological examination revealed an acute inflammatory response and fibrin thrombi within blood vessels in submucosal tissue adjacent to the necrotic epithelium. No HF-related injuries were seen in the trachea or the lungs. In rats surviving to day 14, minimal inflammation with squamous metaplasia of the respiratory epithelium was present in the anterior section of the nose suggesting that regeneration and repair was occurring.

In addition to the above studies, several other acute inhalation studies have demonstrated regional deposition and tissue injury at the site of HF contact by histopathological examination. Morris (1979) assessed the effects of 6 hour inhalation exposures to HF at concentrations of 15, 36, 96, 155 or 197 ppm in rats by histologic examination of the respiratory tract and calculation of lung wet weight-to-dry weight ratios. No evidence of lung damage was found in rats exposed to 15, 36, 96, or 155 ppm HF. However, the 6-hour inhalation exposure to 197 ppm HF killed all animals within a 3 hour postexposure period, yet no signs of pulmonary injury were evident. During exposure, the rats exhibited signs of nasal irritation, mucoid discharge from the nose, sneezing and/or pawing at the nose.

Morris and Smith (1982) investigated the regional deposition of inhaled HF by drawing known amounts of HF (ranging from 40 to 234 ppm) through the surgically isolated upper respiratory tract of anesthetized male Long-Evans rats, while each animal respired room air through an endotracheal tube. For comparative purposes, intact anesthetized rats were subjected to nose-only exposure to 84 ppm HF for 1 hour. Both pulmonary and plasma fluoride concentrations were measured. Results showed that greater than 99.7% HF, at concentrations of 40 to 234 ppm, was drawn into the upper respiratory tract and removed from the air-stream during passage through that site. Plasma fluoride concentrations were significantly elevated by this upper-respiratory tract exposure to HF and were highly correlated with airborne HF concentrations. Both pulmonary and plasma fluoride concentrations were significantly elevated over control levels by nose-only exposure. However, pulmonary fluoride concentrations in nose-only exposed rats were no higher than plasma fluoride concentrations providing little evidence that airborne HF penetrates to the lungs of rats respiring normally.

Stavert et al. (1991) examined the injury in normal nose-breathing rats and in mouth-breathing rats (fitted with endotracheal tubes) that were exposed to 1300 ppm HF for 30-minutes. The rats were euthanized 24 hr after exposures and the upper and lower respiratory tracts were examined histologically and lung gravimetric measurements were performed. Results showed that injury to the respiratory tract of nose-breathing rats was confined to the nasal compartment (particularly in anterior regions of the nasal passages); no lung weight changes or tracheal or lung pathologic evidence was obtained to indicate that HF induced injury occurred more distally. Histological examination showed epithelial and submucosal necrosis, accumulations of inflammatory cells, exudates, and the extravasation of erythrocytes. Results showed higher mortality rates (25% lethality) and major tissue disruption in the trachea of mouth-breathing rats. Histological examination revealed epithelial, submucosal, glandular, and cartilage necrosis, and accumulations of inflammatory cells and exudates. More peripheral lung damage was manifested by lung weight increases and histopathologic changes primarily in the conducting airways. Death was thought to be a result of occlusion of the airways secondary to tracheal injury by HF.

Rosenholtz et al. (1963) determined a 15-minute LC_{50} of 4327 ppm HF in guinea pigs, and 5-, 15-, 30- and 60- minute LC_{50} values of 4970, 2690, 2040, and 1310 ppm HF,

respectively, in rats. Pathological examination was performed on groups of rats exposed in the lethal range for 15 and 30 minute exposures. During exposures to rats, there were signs of irritation of the conjunctivae and nasal passages (reddened conjunctiva, marked lacrimation, pawing at the nose, nasal secretion, and sneezing) which lasted 7 days post exposure. In addition to some delayed deaths, respiratory distress, body weight loss (10-15% during days 3-7 post exposure), and general weakness for several days were seen in some animals. Gross and microscopic examination revealed concentration-dependent lesions in the kidney, liver, nasal passage, bone marrow, and skin. These lesions included selective renal tubular necrosis, hepatocellular intracytoplasmic globules, nasal passage necrosis with associated acute inflammation, possible myeloid hyperplasia of the bone marrow, and dermal collagen changes with acute inflammation. Many of the lesions showed signs of reversibility by 48 hours to 7 days after exposure.

Rosenholtz et al. (1963) also evaluated the effects of sublethal exposures to HF in various animal species and at various periods of exposure. In a group of rats exposed to 1377 ppm HF for 30 minutes, signs of conjunctival and nasal irritation were observed. Body weight changes compared to controls were not significant. Organ to body weight ratios for kidney, liver, spleen, and lung were not significantly different from controls. Because of these findings, only clinical signs of toxicity and pathological changes were studied in subsequent exposure groups. In groups of 20 rats exposed to 2432, 1410, and 490 ppm HF for 5, 15 and 60 min, respectively, signs of toxicity included respiratory distress (lasting for a few hours after exposure), lacrimation, nasal discharge, pawing at the nose, and reddened conjunctiva. In groups of 20 rats exposed to 1438, 590, and 290 ppm HF for 5, 15, and 60 min, respectively, signs of toxicity were less severe than those seen in rats exposed to 50% of the LC_{50}. Signs included ocular and nasal irritation, pawing at the nose, reddened conjunctiva, and sneezing. In groups of 20 rats exposed to 750, 376, and 126 ppm HF for 5, 15, and 60 min, respectively, signs of toxicity included general discomfort, pawing at the nose, and tearing from the nose. Most signs were mild and disappeared within a few hours after exposure. In rats exposed to 307 and 103 ppm HF for 15 and 60 min, respectively, only transient signs of toxicity were observed (pawing at the nose and blinking of the eyes). Tissues (including heart, lung, spleen, kidney, brain, testis, bone marrow, trachea, nasal turbinates, eye, tongue, thymus, adrenal, skeletal muscle, esophagus, stomach, small and large intestine, and pancreas) were taken from 42 rats across groups exposed for 15 min to nonlethal exposures varying from 12.5% to 50% of the LC_{50} values and varying in post-exposure periods from 4 hours to 150 days. Histological examination of these tissues did not reveal any lesions related to HF exposure. The data of Rosenholtz et al. (1963) are summarized in Table 4.

Table 4: Effects of HF Exposures in Rats

Exposures; ppm/min.	Response
4970 ppm / 5 min 2690 ppm / 15 min 2040 ppm / 30 min 1310 ppm / 60 min	LC_{50}
2432 ppm / 5 min 1410 ppm / 15 min 490 ppm / 60 min	(~ 50% LC_{50}) Respiratory distress, lacrimation, nasal discharge, pawing at nose, reddened conjunctivae
1438 ppm / 5 min 590 ppm / 15 min 290 ppm / 80 min	(~ 25% LC_{50}) ocular and nasal irritation, pawing at nose, reddened conjunctivae; signs less severe
750 ppm / 5 min 376 ppm / 15 min 126 ppm / 60 min	(~ 12.5% LC_{50}) general discomfort, pawing at and tearing fro nose; mild symptoms which disappeared with a few hours after exposure
307 ppm / 15 min 103 ppm / 60 min	(~ 10% LC_{50}) pawing at nose and blinking of eyes; transient clinical signs

Groups of 5 rabbits were exposed to 1247 or 854 ppm HF for 15 min. At 1247 ppm, signs of toxicity included lacrimation, nasal discharge, pawing at the nose, reddened conjunctiva, and respiratory distress which lasted for a few hours after exposure. The symptoms disappeared after 4 days. Symptoms were less severe at 854 ppm. Two exposed and two control rabbits were killed and examined histologically. One rabbit exposed to 1247 ppm for 15 min showed alveolar congestion at 14 days after exposure, and one rabbit exposed to 854 ppm for 15 min showed severe intra-alveolar and intra-bronchial hemorrhage when examined two days post exposure.

No deaths occurred in a group of 10 male guinea pigs exposed to 1377 ppm HF for 30 min. No pathological examinations were performed.

Two dogs each were exposed to 666 or 460 ppm HF for 15 min. Dogs exposed to 666 ppm showed signs of general discomfort, blinking, sneezing, and coughing. Coughing persisted to day 7 and 10 after exposure. Dogs exposed to 460 ppm showed a mild eye irritation and sneezing, and developed a dry cough lasting 2 days. For both exposures, hematologic data (hematocrit and blood cell counts) showed no significant changes compared to pre-exposure values. Two dogs each were exposed to 243 or 157 ppm HF for 60 min. Dogs exposed to 243 ppm showed signs of general discomfort, blinking, sneezing, and coughing. Coughing persisted to day 7 and 10 after exposure. Dogs exposed to 157 ppm showed mild eye irritation and sneezing, and dry cough lasting 2 days. For both exposures, hematologic data showed no significant changes compared to pre-exposure values.

Machle et al. (1934) investigated the effects of HF in groups of 3 guinea pigs and 3 rabbits by exposing them to concentrations ranging from 30 to 9760 ppm at durations ranging from 5 minutes to 41 hours. Results indicate an approximate LC_{100} for guinea pigs and rabbits of 9760 ppm for a 5-minute exposure, >4000 ppm for a 15-minute exposure, >1220 ppm for a 2-hour exposure, and >976 ppm for a 3-hour exposure. In guinea pigs, irritation of the respiratory tract was observed at all concentrations and exposure periods. Signs of irritation included closed eyes, coughing and sneezing, mucoid conjunctival and nasal discharges, and slowing of the respiratory rate, Exposures above 1830 ppm HF resulted in damage to the conjunctiva and nasal turbinates, pulmonary hemorrhage, and in some cases bronchopneumonia, and death. Guinea pigs showed a tendency to delayed responses, as death occurred between the 5th and 10th week post exposure. Guinea pigs exposed to 1220 ppm or less for 30 minutes survived, but appeared weak and ill. Pathological examination revealed injury to the cornea and nasal mucous membranes, cardiac dilatation with congestion and myocardial injury, pulmonary hemorrhage, congestion, emphysema, and edema and bronchopneumonia, and hepatic, splenic and renal congestion. A concentration of 122 ppm HF was tolerated for approximately 5 hours, producing only mild irritation to the respiratory tract. No deaths occurred in guinea pigs exposed to 30 ppm, 6 hours/day for approximately 5 days (or 41 hours total exposure). No specific toxicity data were given. Exposure of rabbits to 1830 ppm HF or greater resulted in respiratory tract damage and death. Rabbits exposed to 1220 ppm or less for as long as 30 minutes survived. A concentration of 122 ppm or less was tolerated for approximately 5 hours "without injury severe enough to cause death." No deaths occurred in rabbits exposed to 30 ppm, 6 hours/day for approximately 5 days (or 41 hours total exposure). Eighteen hours after the last exposure, pathological examination of one rabbit showed liver and kidney damage and evidence of fibrosing processes in emphysematous lungs.

Wohlslagel et al. (1976) exposed groups of 10 male Sprague-Dawley rats and 10 CF-1 mice to various concentrations of HF for 60 minutes and observed them for signs of toxicity and mortality during a 14-day period after exposure. An LC_{50} for each species was calculated. For rats, an LC_{50} value of 1395 (1302-1495) ppm was calculated. A concentration of 1087 ppm was not lethal (0/10 deaths), whereas, a concentration of 1108 ppm resulted in 2/10 deaths. Pathological examination of rats dying during or after exposure showed pulmonary congestion, intra-alveolar edema and some cases of thymic hemorrhage. For mice, an LC_{50} value of 342 (315-372) ppm was calculated. A concentration of 263 ppm was not lethal (0/10 deaths), whereas, a concentration of 278 ppm resulted in 1/10 deaths. Pathological examination of mice dying during or after exposure exhibited pulmonary congestion and hemorrhage. Symptoms of rats and mice during exposure included eye and mucous membrane irritation, respiratory distress, corneal opacity and erythema of exposed skin.

DiPasquale and Davis (1971) and Higgins et al. (1972) reported an investigation evaluating the toxicity of halogen acid gases resulting from combustion or pyrolysis of aircraft interior materials. Exposures were for short periods of time as might be

experienced in the evacuation of a burning aircraft. Ten Wistar rats and 15 ICR mice per group were exposed to a series of HF concentrations to determine 5-minute LC_{50} values. Animals were observed for a 7 day period post exposure. A 5-minute rat LC_{50} value of 18200 (15965 - 20748) ppm was calculated. A 5-minute mouse LC_{50} value of 6,247 (4789 - 8149) ppm was calculated. A 5-minute exposure to 2430 ppm HF was not lethal to a group of 15 mice. HF produced pulmonary edema of varying degrees of severity in most of the exposed animals. For exposures above the LC_{50}, pulmonary hemorrhage was a common finding in animals that died during or shortly after exposure. For exposures below the LC_{50}, delayed deaths occurred about 24 hours after exposure; occasionally deaths occurred 3 to 4 days later.

B. Human Studies

Machle et al. (1934) investigated the effects of HF on two male human volunteers exposed to 32, 61, and 122 ppm for very short exposure periods. Two men tolerated exposure to 32 ppm HF for a 3-minute period, but experienced discomfort and smarting of the nose and eyes. They did not cough or sneeze even though there was an irritation of the larger air passages. Two men exposed to 61 ppm HF showed marked nasal irritation and definite conjunctival irritation. They experienced tickling and discomfort in the larger air passages with each inspiration and the taste of the gas was definite. Two men tolerated exposure to 122 ppm HF for more than 1 minute (exact time was not given). They experienced definite smarting of the skin within one minute. Conjunctival and respiratory irritation were marked, but tolerable, and the taste of the gas was pronounced.

An experimental study in 20 male volunteers showed a dose-dependent relationship between concentrations of inhaled HF and plasma fluoride (Lund et al., 1997). Three groups of subjects were exposed to HF concentrations of 0.66-0.49 ppm (n=9), 0.57-1.96 ppm (n=7), and 4.25 ppm (n=7). Each group was exposed for a 60 minute period; 45 minutes resting and the final 15 minutes exercising. Plasma fluoride levels were measured before, during and after exposure. Scores for irritation symptoms of the eyes and lower and upper airways were recorded before the start of exposure, after 30 and 60 min of exposure, and 4 and 24 hours after the end of exposure. Lung function, forced expiratory volume (FEV_1) and forced vital capacity (FVC) were measured by spirometry before exposure, every 15 min during exposure, immediately after exposure, 30 min after exposure, and every hour thereafter until 4 hours after exposure.

A significant increase in concentration of fluoride in plasma (C_{max}) was detected in the groups exposed to 0.57-1.96 ppm and 1.96 - 4.25 ppm HF, but not in subjects exposed to 0.16 - 0.49 ppm. At exposures between 1.96 - 4.25 ppm, C_{max} was recorded at 60 min (3 subjects), 90 min (3 subjects) and 120 min (1 subject) after the start of exposure. At exposures over 1.96 ppm, C_{max} occurred 60 min (5 subjects) and 90 min (2 subjects) after the start of exposure. The plasma concentration of fluoride then declined but was still high 180 min after the start of exposure compared to baseline measurements of all subjects except one subject. Symptoms from the upper airways were most pronounced, and a significantly higher prevalence of total symptom scores and symptoms of the upper

airways were found for exposure to HF over 1.96 ppm compared with 0.16-0.49 ppm and 0.57-1.96 ppm. Linear regression analysis did not detect an association between FVC or FEV_1 and plasma fluoride levels. The authors concluded that concentrations of HF should be kept below 1.96 ppm to avoid symptoms of the upper airways and eyes.

Lee et al. (1993) report the results of prompt treatment of thirteen oil refinery workers accidentally exposed to a maximum concentration of 150-200 ppm hydrofluoric acid mist for about 2 minutes. Nebulized calcium gluconate (4 mL of a 2.5% calcium gluconate solution mixed in normal saline and delivered with 100% oxygen) was used for treatment. Subsequent to treatment the patients received medical evaluation within 1 hour of exposure. Respiratory symptoms consisted of minor upper respiratory tract irritation; the majority of patients were asymptomatic. No patient showed evidence of skin or eye burns.

II. *Respiratory Sensory Irritation*

The proposed test rule for HAPs recommends that a respiratory sensory irritation test using American Standard Test Method (ASTM) E 981-84 be conducted to provide a quantitative estimate of the sensory irritant potential of HF. This test detects irritation by a characteristic change in the breathing pattern of mice, resulting in a reduction in the breathing rate during exposure to a test atmosphere. Sensory airway irritation is any sign that a chemical substance is stimulating the nerves of the respiratory tract as identified by the characteristic pause during expiration in the respiratory sensory irritation test.

The HF Panel is of the opinion that this study is not necessary because there exists a nucleus of acute inhalation toxicity data (see Acute Inhalation Section) that can be used to make educated estimations of adverse effects resulting from acute HF accidental exposures. In fact, both the AIHA's Emergency Response Planning Guide (ERPG) committee and the U.S. EPA National Advisory Committee for Acute Exposure Guideline Levels (AEGLs) have successfully used these data to make recommendations for emergency response planning guidelines related to HF accidental releases and exposures. (AIHA, 1991; Talmage, 1997.) Furthermore, the HF Panel believes that a respiratory sensory irritation study with HF is not necessary because:

1) HF was assessed for sensory irritation potential in mice by ICI (CTL, 1990). Results estimated a RD_{50} of 151 ppm. Three groups of mice were exposed to HF concentration of 28, 129, or 172 ppm for 30 min. Respiratory depression was measured and the RD_{50} determined according to the method of Alarie (1981).

2) The acute inhalation study in rats performed by Stonybrook Laboratory (1996), including several pulmonary function parameters, further characterizes the respiratory irritation potential of HF. Results of this study are summarized below:

The Stonybrook Laboratory (1996) study included groups of rats that were used to measure pulmonary resistance, functional residual capacity, quasistatic pressure-volume curves,

maximum forced exhalations, and single-breath carbon monoxide diffusing capacity. As indicated in Table 1, several pulmonary function parameters were altered which were consistent with changes in the airways, particularly increased pulmonary resistance (Rpul) and decreased flows in the maximal forced exhalation maneuver (FEV). A concentration-response relationship for pulmonary alteration was observed in (Table 1). The relative inability of lungs to deflate in the pressure-volume curves in animals exposed to 4887 and 8621 ppm HF for 2 minutes, and 1764 ppm HF for 10 minutes, may have resulted from obstruction of small airways constricted at lower lung volumes. Single breath carbon monoxide diffusing capacity (Dlco) was significantly decreased in lungs of animals exposed to 8621 ppm HF for 2 minutes. Dlco was only marginally decreased in animals exposed to 1764 ppm HF for 10 minutes. Flow near the end of the maximal forced exhalation (FEV), when 75% of the forced vital capacity had been exhaled, was significantly decreased in lungs of animals exposed to 8621 ppm for 2 minutes. A marginal decreased FEV was measured in lungs of animals exposed to 4887 ppm for 2 minutes, and to 1764 ppm for 10 minutes. This flow represented effects in the lower airways (alveolar involvement).

In summary, the HF HAPS Group does not concur with the requirements for acute inhalation toxicity and respiratory sensory irritation testing proposed under EPA's HAPs Test Rule. Based on available acute inhalation toxicity data and on recent unpublished research on the effects of acute inhalation exposure to HF, the HF Panel believes that no additional acute inhalation testing is needed. The HF Panel believes that adequate toxicological data exist to estimate risks related to acute inhalation exposures to HF. In fact, both the AIHA ERPG Committee and the National Advisory Committee for AEGL, sponsored by the U.S. EPA, have reviewed the existing acute toxicity data on HF and have successfully made recommendations for emergency response planning guidelines.

III. *Subchronic Toxicity*

In the proposed rule, EPA has requested a subchronic 90-day study with HF. Although a 90-day inhalation study has been reported, there were several inadequacies in this study, *e.g.*, the atmosphere generation system and inconsistencies with existing data. In consideration of these inadequacies, the HF Panel submitted a proposal to examine the relationship between oral and inhalation exposure and the induction of systemic toxicity. As part of that proposal, we would determine the concentration times time (CxT) relationship for HF over a period of 28 days that would include periodic sacrifices for clinical pathology and pathology evaluations. With these data and comparison with data developed from oral toxicity studies with sodium fluoride, an adequate characterization of the subchronic effects of the fluoride ion could be accomplished. Since the potential systemic effects of HF are due to fluoride ion, use of oral sodium fluoride data as basis for evaluating the risk to HF is appropriate. A brief review of the 90-day inhalation study and subchronic oral toxicity studies with sodium fluoride and the chemistry of HF are provided. Because the data indicate that HF toxicity is due to short-term exposures, a 28-day inhalation study would be sufficient to characterize the CxT relationship for HF.

At the site of entry or in contact with moisture in air, anhydrous HF instantaneously and strongly associates with water in the tissues, forming hydrofluoric acid which is a weak acid and may not be fully ionized. It is non-ionic HF, and not fluoride ion, which is more readily transported across cell membranes of all compartments of the body, *e.g.*, from lungs or skin into the blood. For this reason, ingested fluoride is more rapidly absorbed in the stomach (acidic pH) than in the intestines (alkaline pH). It is the concentration gradient of non-ionic HF that is the driving force for HF transport across biomembranes. In transmembrane fluoride transport, non-ionic HF is the primary permeating species (Whitford, 1983; Ekstrand, 1996).

The extent of ionization of HF is governed by the Henderson-Hasselbach equation. In pure water solution, HF is partially in molecular form and partially ionized. However, in the extracellular fluid at pH 7.4, HF (pK_a=3.45) is essentially completely ionized (HF:F = 1:9000). In essence, the HF, as such, does not exist at pH 7.4. Because of the buffering capacity of the body, the 1:9000 ratio is the same whether HF or sodium fluoride (or another soluble fluoride) is introduced into the extracellular fluid. Because of the ionic nature of the reaction, HF will be very rapidly converted to fluoride. This is indistinguishable from sodium fluoride and will have the same physiological distribution and potential toxicity.

In a 90-day subchronic study (Placke and Griffin, 1991) female and male rats (20/group) were exposed to HF concentrations of 0.1, 1.0 or 10 ppm for 6 hours/d, 5 days/week. Observations included clinical signs, body weight, organ weights of liver, kidneys, testes, ovaries, adrenals, heart, spleen, brain and lungs, hematology, blood biochemistry and complete histopathology. Five males and one female rat were found dead during the study in the 10 ppm group. Clinical signs in this group were red-colored discharge from eyes and nose, ruffled fur, alopecia and hunched posture. At 10 ppm, body weights were depressed and in 9 males and 2 females, dental malocclusions were observed. Increases in the number of segmented neutrophils were seen in the high dose male group. Platelets were increased in the high dose males. Mid- and high-dose group males showed decreased numbers of lymphocytes, and RBCs were depressed in high dose males and females. Biochemistry showed decreased serum glucose in the high dose males. Additionally, decreases were seen in serum albumin (high-dose males and females), A/G-ratio (mid-and high-dosed males), and increases were seen in potassium and inorganic phosphorous in both males and females of the high dose groups. Relative organ weights of kidneys, liver, lung, testes, spleen, brain, heart and adrenals were increased at the highest dose. Histopathological changes were not found. The decreases in serum A/G ratio and lymphocytes in the male mid-dose group were too small to have a biological significance and are, therefore, not considered as adverse effects. Thus, the NOAEL in this study was 1.0 ppm.

In addition to the 90-day inhalation study with HF, several subchronic oral toxicity studies have been conducted with sodium fluoride. Many of these studies, however, were conducted prior to implementation of GLPs and were designed primarily to investigate the effect of fluoride administration on tooth development (fluorosis). Thus, these studies were limited in scope and are not considered in this review.

The National Toxicology Program (NTP) conducted repeated oral exposure studies in rats and mice (NTP, 1990). Two-week, 6-month and 2-year studies were conducted in which sodium fluoride was administered via drinking water. Only the 6-month subchronic study will be reviewed.

Male and female F344 rats (n=10/sex/dose group) or B6C3F1 mice (n=8-12/sex/dose group) were administered sodium fluoride in deionized water for 6 months. Rats were administered concentrations of 0, 10, 30, 100 or 300 ppm, and mice were administered concentrations of 0, 10, 50, 100, 200, 300 or 600 ppm. Three control groups were also utilized and consisted of:

- male and female rats and mice provided deionized water and low ($\leq$2.1 ppm) fluoride semi-synthetic diet,
- male and female rats and mice provided sodium chloride supplemented water and low semi-synthetic diet, and
- male and female rats and mice provided deionized water and standard (NIH-07) diet.

During the study, the animals were observed twice daily for mortality and morbidity and weighed weekly. Food consumption was determined every other week for the first 13 weeks and then weekly through the remainder of the study. Water consumption was recorded daily. Blood, urine and bone fluoride levels were determined prior to and at termination of the study. At termination, gross examinations were conducted on all animals, and histological examinations were conducted on tissues of rats and mice in the control groups and in rats and mice at the two highest sodium fluoride concentrations.

Food and water consumption were lower in high-dose males and females compared to controls. The fluoride content of bone and urine increased with increasing fluoride concentration in the drinking water. The fluoride content of plasma was significantly increased only in the high-dose groups and in the group of male rats maintained on the standard NIH-07 diet over that of control rats maintained on the low fluoride semisynthetic diet. The principal pathological effect associated with the administration of sodium fluoride for 6 months was observed in the incisor teeth and stomach. Five male rats receiving 300 ppm sodium fluoride had focal or multifocal degeneration of the tooth enamel, primarily in the maturation zone near the apical end of the incisor tooth. In a few animals, small aggregates of enamel-like material were trapped within the cell layers. These changes collectively were diagnosed as dysplasia.

On gross examination, the mucosa of the glandular stomach of most male rats receiving 300 ppm sodium fluoride appeared thickened, and focal or multifocal hemorrhages were observed. Similar but less severe alterations were observed in some rats receiving 100 ppm sodium fluoride. A perforated ulcer of the glandular stomach was seen in a 300 ppm female, and multiple small nonperforated ulcers were seen in one 300 ppm male. Histologically, a subtle focal to diffuse hyperplasia of the mucosal epithelium of the glandular stomach was observed in most male and female rats receiving 300 ppm. This was accompanied by minimal individual cell necrosis (apoptosis) and was most evident in the pyloric region. Nearly all rats receiving 300

ppm sodium fluoride had focal basal cell hyperplasia of the stratified squamous epithelium adjacent to the limiting ridge (junction of the glandular stomach and forestomach). Hyperplasia of the mucosal epithelium of the glandular stomach also was observed in half the males and in two females receiving 100 ppm sodium fluoride, but individual cell necrosis was not. No other histologically significant pathological changes were observed in this study.

Groups of 8 to 12 mice of each sex were administered 0, 10, 50, 100, 200, 300, or 600 ppm sodium fluoride in deionized water *ad libitum* for 26 weeks. The study design was similar to the design utilized for the 6-month study with rats. All but one early death occurred in the high-dose groups: four high-dose males died during weeks 13 and 14; one male mouse in the second highest dose group died during week 19; nine high-dose females died during weeks 8 to 18. All other mice survived to scheduled termination. Among the 13 high-dose animals that died before the scheduled sacrifice, six were killed because they were moribund. Signs of toxicity (thin appearance, hunched posture, weakness) were observed in only two of these before they became moribund. Mice exposed to the four highest doses of sodium fluoride had chalky white teeth. The lower incisors were more affected than upper incisors, and some teeth in mice in the two highest dose groups were chipped. No other signs of toxicity were observed in any of the animals that died early or that survived to the end of the study.

Body weight gain was depressed in the three highest dose groups for both sexes, and was consistent with the observed decreases in food consumption. Average weekly feed consumption was within 20% of control values for all groups, except high-dose males which consumed only 77% of that consumed by controls. Average weekly water consumption was within approximately 20% of control values for all dosed groups.

The fluoride content of bone and urine was increased in a dose-related fashion with increasing fluoride concentrations in the drinking water. The fluoride concentration in plasma appeared to increase with the dose of fluoride, but the necessity of pooling samples to obtain sufficient material for analysis prevented performance of meaningful statistical analyses of these data. A number of histological alterations were identified in mice dying early or sacrificed while moribund and consisted primarily of acute nephrosis, the likely cause of death in these mice.

Compound-related effects were observed in the femur and, to a lesser extent, in the tibia of nearly all male and female mice receiving 100 to 600 ppm sodium fluoride and 5/10 males receiving 50 ppm. In mice receiving 600 ppm some lamellae appeared thicker and more irregular with cement lines that were less prominent and smooth in contour. The osteoid seams lining some osteons (haversian canals) of the cortical bone were increased in thickness. These changes were not uniform or diffuse. In mice receiving 50 or 100 ppm only occasional prominent osteoid seams were evident. Lesions of the lower incisors were generally more extensive in the mice receiving 300 or 600 ppm than in mice receiving lower doses. The enamel from the affected mice that were examined had focal or multifocal irregularity of the layer of ameloblasts, with projections and folds that sometimes surrounded isolated islands of enamel. In some mice, there was loss of the surface columnar cells and variable loss of cells from the stratum intermedium. The remaining cells were reduced in size and disorganized. These changes collectively were diagnosed as dysplasia.

IV. *Developmental Toxicity*

No specific studies on the developmental toxicity of HF have been reported. However, systemic toxicity due to HF and sodium fluoride are related to the *in situ* generation of fluoride ion. Therefore, developmental toxicity studies for sodium fluoride would be an appropriate surrogate for any assessment conducted for HF. Developmental toxicity studies have been reported for rats and rabbits in which the compound was administered via drinking water (Collins et al., 1995; Heindel et al., 1996).

In the study of Collins et al. (1995), pregnant rats (n=35-37/group) were administered 0, 10, 25, 100, 175 or 250 ppm sodium fluoride in drinking water throughout gestation. On a mg sodium fluoride/kg body weight basis, the dose levels were 0, 1.4, 3.9, 15.6, 24.7 and 25.1 mg/kg. Reduced food was considered due to poor palatability of sodium fluoride at these concentrations. No effects on reproductive outcome, and no biologically significant developmental effects were observed in this study. A decrease in the mean number of implants per litter was observed in the 250 ppm group, and is related to a decline in the number of corpora lutea. A statistically significant increase in the number of fetuses with three or more skeletal variations was observed in offspring of dams administered 250 ppm sodium fluoride. However, the number of litters containing fetuses with three or more skeletal variations was not statistically increased. Thus, sodium fluoride was not teratogenic.

In a study reported by Heindel et al. (1996), pregnant rats (n= 26/group) were administered 0, 50, 150 or 300 ppm sodium fluoride in deionized drinking water during days 6-15 of gestation; dose levels were 6.6, 18.3, or 27.1 mg of sodium fluoride/kg body weight. Also, pregnant rabbits (n= 26/group) were administered 0, 100, 200 or 400 ppm sodium fluoride in deionized drinking water during days 6-19 of gestation; dose levels were 10.3, 18.1 or 29.2 mg sodium fluoride/kg body weight. Declines in body weights and food consumption were observed in the high dose groups for both rats and rabbits, and were attributed to decreases in water consumption due to poor palatability of sodium fluoride in drinking water. No effects on reproductive outcome (implantations, corpora lutea, etc.) were observed in either species. Also, no effects on fetal body weights or developmental malformations were observed in either species.

As part of this study, these investigators collected serum during gestation and measured total fluoride levels. Oral administration of sodium fluoride at concentrations of up to 400 ppm in rabbits resulted in blood fluoride levels of 0.7 mg/mL. Further, the data suggest that oral absorption in the rabbit at about comparable doses, in mg F/kg body weight, is about an order of magnitude greater in rabbits than rats.

In summary, these studies reveal that sodium fluoride does not induce developmental toxicity in rats or rabbits at levels up to 400 ppm (29.2 mg sodium fluoride/kg body weight) in drinking water, even at levels that produced maternal toxicity.

V. *Reproductive Toxicity*

No specific reproductive toxicity data on HF are available. However, as discussed above for both subchronic and developmental toxicity studies, reproduction studies with sodium fluoride would be appropriate for an assessment of the potential reproductive effects due to HF.

The effect of sodium fluoride on fertility has been studied in mice, rats and rabbits (Araibi et al., 1989; Chinoy et al., 1991; Chinoy and Sequeira, 1989; Chinoy and Narayana, 1994). Fluoride, administered by gavage or through the diet, reduced male fertility and caused histological changes in sperm cells at oral doses of about 5 mg sodium fluoride/kg body weight. Oral administration of sodium fluoride to B6C3F_1 mice were at 70 mg/kg sodium fluoride for five consecutive days had no effect on spermatogenesis (Li et al., 1987). In a second study, B6C3F_1 mice were maintained on 75 ppm or sodium fluoride in drinking water for 21 weeks with no effects on spermatogenesis (Dunipace et al., 1989). Intratesticular injection of sodium fluoride (Sprando et al., 1996) at doses of 0, 50, 175 or 200 ppm produced no changes in sperm morphology or spermatogenesis; dose equivalents were 0, 0.011, 0.037 and 0.042 mg sodium fluoride/kg body weight, respectively.

In a 2-generation reproduction study, female mice received 0, 110, 220, 440 mg/L sodium fluoride in their drinking water and were mated with untreated males (Messers et al., 1973). In the control group, a progressive decline in litter production with successive litters occurred in both generations. By 6 weeks of treatment, about 50% of the females in the highest dose group had died and by week 17 of exposure all females in this group had died. Also, in the 110 mg/L dose group only nine litters were born over a 10 week period. This study is considered to be of limited design.

In a 3-generation study, female mice of the first generation were orally exposed to 0 or 2 mg F/kg as NaF, equivalent to 0 and 0.3 mg F/kg body weight /day, respectively, and mated with untreated males (Tao and Suttie, 1976). The second and third generation females received 0, 2 and 100 mg F/kg diet. Relevant observations included among others, growth, reproductive response, litter size, pup weight and incidence of stillbirth. No compound-related effects on these parameters were observed. The protocol of this study is considered incomplete and kidney infection may have disturbed the sensitivity of the test.

In an unpublished two-generation reproduction study (cited in Sprando et al., 1996), rats were administered 0, 25, 100, 175 or 250 ppm sodium fluoride in drinking water for approximately 14 weeks (10 weeks of pretreatment, 3 weeks of mating and 1 week of post-weaning). No significant reproductive differences between treated or control animals were reported, and no effects on sperm count, testis weight, testicular pathology or hormonal parameters (LH, FSH or testosterone) were indicated. However, the full report was not available for critical review.

Although decreases in fertility were observed in mice administered sodium fluoride by gavage or through the diet, other studies conducted under more rigorous conditions and at higher doses, on a mg sodium fluoride/kg body weight basis, indicate that this material is not a reproductive toxicant. Therefore, conducting additional reproduction toxicity studies with HF would not improve the quality of available information.

VI. *Neurotoxicity*

Neurobiological studies have suggested a variety of basic mechanisms by which fluoride ion can affect the function of the nervous system. Although these studies do not specifically address the issue of neurotoxicity, they do establish the fluoride ion concentration range that is required for biological impact on the nervous system and elucidate the function of fluoride ion which is a normal constituent of cerebrospinal fluid. Kay et al. (1986) found that fluoride ion can beneficially stabilize the operation of voltage-dependent calcium (Ca++) channels in neurophysiological experiments. Jope and Lally (1988) demonstrated that 12 mM fluoride was required to stimulate Ca++ influx in synaptosomes. The enhanced Ca++ influx was ATP-independent. There are a number of possible mechanisms for this effect, but Jope and Lally (1988) favor the hypothesis that fluoride ion directly activates a guanine nucleotide binding protein associated with receptor-gated Ca++ channels.

Increased intracellular concentration of unbound Ca++ can influence a number of basic neuronal processes including protein phosphorylation, activation of proteases, neurotransmitter release, and perhaps neuronal growth. Nakagawa-yagi et al. (1993), for example, studied the growth of cells maintained *in vitro* and found that fluoride ion could inhibit neurite outgrowth. This inhibitory effect was blocked by Mn++ which is a non-specific blocker of Ca++ entry. The effect of fluoride ion on neurite growth is therefore probably mediated by its ability to increase intracellular Ca++. In summary, the available neurobiological data suggest that fluoride ion affects neuronal functions by its influence on Ca++ flux across neuronal membranes.

Since fluoride has the ability to affect key neurobiological process such as Ca++ flux, it is perhaps not surprising that relatively high exposure concentrations of sodium fluoride *in vivo* have been reported to alter behavior of rats. The behavioral effects, however, are quite subtle. Mullenix et al. (1995) studied the effects of 100 ppm of sodium fluoride in drinking water for six weeks in male and female rats. The amount of sodium fluoride that can be administered subchronically is limited by the high incidence of death associated with dehydration that is apparent with 175 ppm exposures. The authors conducted a detailed analysis of the number of initiated behaviors, the total duration of specific behaviors, the temporal distribution, i.e., whether behaviors were clustered or dispersed in time, of specific behaviors, and the temporal distribution for sequences of different types of behavior. The analysis involved over 100 dependent variables for each rat for each category of initiations, duration, and temporal distribution. Whereas the male rats were not affected, females showed several statistically significant differences relative to control. Sodium fluoride treated females had fewer initiations of sitting behavior, grooming-attention sequences, grooming-exploration sequences, and there was increased temporal clustering of grooming-attention sequences. The vast majority of the hundreds of other measures were apparently not significantly affected.

Similar behavioral changes were noted in rats that were exposed during gestation or neonatally, and despite a few differences, the effects and their magnitude were not markedly different from adult exposures. The developmental studies did provide important additional information in that 75 ppm was identified as an exposure concentration without identifiable behavioral effects. Potential concern about developmental exposures should therefore be similar to the level of concern that might be associated with adult exposures. Unfortunately, the extent of concern is difficult to judge

because it is unclear how to interpret the toxicological importance of the effects described by Mullenix et al. (1995). Changes in the temporal clustering of a specific behavioral sequences such as grooming followed by paying attention to a location in the cage, for example, is not obviously maladaptive for the rat and is not considered significant.

The behavioral measurements in the Mullinex et al. (1995) study are far more complex than the simple parameters that comprise the functional observational battery and motor activity assessments in regulatory neurotoxicology studies. Protocols conducted under applicable EPA neurotoxicology test guidelines can detect gross phenomena such as tremors and ataxia or substantial (30-40%) increases and decreases in the amount of motor activity. The behavioral changes described by Mullinex et al. (1995), however, are simply too subtle to be among the kinds of effects that a standard neurotoxicology study has the precision to measure. It is furthermore unlikely that the neuropathological evaluation conducted under guideline tests would reveal any structural anomalies that were not detected during a standard 90-day toxicology study (Placke and Griffin, 1991) which included microscopic evaluation of brain tissue by standard pathological methods. (See also NTP, 1990.)

Conducting EPA guideline neurotoxicology tests is not necessary because such studies would not increase the ability of the EPA to identify and assess any risk that might be associated with exposure to fluoride. The request for standard neurotoxicology studies should be deleted from the testing requirements for the reason that such studies would not improve the quality of information that is already available.

VII. *Immunotoxicity*

Although there are no specific studies to evaluate the immunotoxicity of inorganic fluorides, there are data from repeated dose studies in animals with HF and inorganic fluorides and from epidemiological studies of communities with fluoridated water supplies indicating that fluoride does not produce immunotoxic effects.

Rats were exposed to HF at 0, 0.1, 1.0 or 10 ppm for 91 days (Placke and Griffin, 1991; see Subchronic Toxicity Section). No histopathological effects were reported in the spleen, thymus or bone marrow. The slight changes in several hematological parameters, e.g. decreased lymphocytes, increased white blood cell counts, were judged by the study authors as having minimal toxicological significance, and these effects were probably secondary to the decreased food consumption and the dental malocclusion noted in the animals.

Numerous epidemiology studies have been conducted in communities with fluoridated water supplies, with no indication that immunosuppression, and a consequent increased sensitivity to infection or other disease, could be associated with fluoride exposures. In addition, the American Academy of Allergy concluded that no suggestions of any immune reactions occurred with oral exposure to fluoride (cited in ATSDR, 1993).

At least four chronic bioassays have been conducted with sodium fluoride. Mice were exposed to sodium fluoride in their drinking water for two years to 25, 100 or 175 mg/L, or in their feed to 4,

10 and 25 mg/kg/day. Hematological and histopathological examinations did not suggest any immunological involvement in these studies. A similar lack of immunological involvement was noted in two chronic rat studies with dose levels up to 4.29 mg F/kg/day in a drinking water study, and 11.24 mg F/kg/day in a feeding study (NTP, 1990; Maurer et al. 1990; Maurer et al. 1993). In the NTP drinking water studies with rats and mice, histopathological evaluation included mandibular and mesenteric lymph nodes, bone marrow, spleen and thymus at 24 and 66 weeks, and at study termination at 105 weeks. Hematology measures, performed at 24 and 66 weeks in rats and at 24 and 66 weeks in mice, included white blood cell count with differentials and platelet counts. No toxicologically significant findings were observed in these studies.

There are two major consequences associated with immunosuppression in animals or man. The most common is an increased susceptibility to infections by bacteria, viruses, fungi and parasites. A frequent complication is an increased incidence of cancer.

Numerous epidemiology studies have examined the relationship between fluoridated water and cancer (reviewed in ATSDR, 1993). The weight of evidence strongly suggests that no relationship exists. One of the most recent and thorough studies examined >2,300,000 cancer deaths and >125,000 cancer cases in U.S. counties exposed to artificially fluoridated drinking water for up to 35 years (Hoover et al., 1991, as cited in ATSDR, 1993). No relationship between cancer incidence or mortality and duration of fluoridation was found. In addition, one study reported an inverse relationship between fluoride levels and cancer of the oral cavity and pharynx for populations in Norway (ATSDR, 1993).

In conclusion, data from numerous epidemiology studies of populations exposed to fluoridated drinking water, extensive histopathological and hematological examinations from four lifetime dosing studies with sodium fluoride in rats and mice and a 90-day inhalation study with HF in rats, do not show an association with increased susceptibility to infection, increased mortality or carcinogenicity and do not suggest that fluorides are immunotoxic.

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APPENDIX II

ALTERNATIVE TESTING PROPOSAL

CHEMICAL MANUFACTURERS ASSOCIATION

LANGLEY A. SPURLOCK, PH.D., CAE
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November 22, 1996

Charles M. Auer, Director
Chemical Control Division
Office of Pollution, Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W., Mail Code 7405
Washington, DC 20460

Re: Proposed Test Rule for Hazardous Air Pollutants (61 Fed. Reg. 33178, June 26, 1996); OPPTS-42187A: FRL-4869-1

Dear Mr. Auer:

The Chemical Manufacturers Association's Hydrogen Fluoride (HF) Panel is pleased to provide the enclosed proposal for a physiologically-based pharmacokinetic (PBPK) model to evaluate potential hydrogen fluoride (HF) toxicity.

The HF Panel believes that the high water solubility of HF will lead to almost complete deposition of inhaled HF in the nose. The Panel therefore proposes to conduct an inhalation study to investigate nasal toxicity and limited systemic toxicity of HF. Concurrently, the Panel will develop a dosimetry model for HF uptake in the nose.

The HF Panel believes that the known chemistry and metabolism of HF makes it appropriate to use pharmacokinetic data on the fluoride ion when considering HF systemic toxicity. If the inhalation study indicates systemic toxicity of HF, there are sufficient data on HF and soluble fluorides to address many of the endpoints identified by EPA in the proposed rulemaking.

The HF Panel expects that this proposal will form the basis for developing an Enforceable Consent Agreement (ECA) with the Agency, and welcomes the opportunity to meet with EPA to develop the details of the ECA. Nevertheless, the Panel reserves its rights to file comments on the proposed rule and, if necessary, to challenge the legal and scientific basis of the Agency's proposed testing of HF.

If you have any questions concerning the information contained in the attached document, please call Elizabeth Festa Watson, Manager of the HF Panel, at 703-741-5629.

Sincerely,

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1300 WILSON BOULEVARD, ARLINGTON, VA 22209 • TELEPHONE 703-741-5600 • FAX 703-741-6091

BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

PROPOSAL FOR A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL FOR HYDROGEN FLUORIDE

Submitted by

THE HYDROGEN FLUORIDE PANEL OF
THE CHEMICAL MANUFACTURERS ASSOCIATION

Proposal for Pharmacokinetic Modeling Under the Proposed Test Rule for Hazardous Air Pollutants 61 Federal Register 33178 June 26, 1996	Docket No. OPPTS-42187A

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PROPOSAL FOR A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL FOR HYDROGEN FLUORIDE

Executive Summary

EPA has proposed that a variety of tests be conducted on hydrogen fluoride (HF) under Section 4 of the Toxic Substances Control Act, including acute and repeated exposure studies, developmental and reproductive toxicity, immunotoxicity and neurotoxicity studies (see 61 Fed. Reg. 38446, July 24, 1996). As part of its proposed test rule for Hazardous Air Pollutants (HAPs), the Agency has invited industry to submit proposals for physiologically-based pharmacokinetic (PBPK) studies to allow for species-to-species and route-to-route extrapolations as a method for satisfying some of the Agency's proposed testing requirements.

This proposal describes the development of an air flow model in the rat nasal cavity and upper respiratory tract (URT) to examine the portal-of-entry effects. This model, which is described in greater detail below, will be validated with histopathological mapping of the URT following inhalation exposure to rats. From these data and computational fluid dynamics mapping of flux to tissue surfaces of HF, computational models will be developed to estimate flux in the human nasal cavity.

Data indicate that, under physiological conditions, the fluoride (F^- ion) is the species of interest, regardless of whether the F^- is contributed by HF or by a soluble fluoride, e.g., sodium fluoride. At the air:tissue interface, HF will come in contact with tissue components and then enter the body as HF. Once absorbed, HF dissociates to the F^-. This dissociation is extremely rapid, and at a physiological pH of 7.4, dissociation of HF to the F^- is strongly favored. Following absorption, the distribution, metabolism and toxicity of the F^- is the same as that following gastrointestinal absorption of a soluble fluoride, e.g., sodium fluoride. Sodium fluoride is converted to HF and is absorbed from the acid environment of the stomach, after which it rapidly dissociates to the F^-. Given the known chemistry and metabolism of HF, the HF Panel believes that it is appropriate to use pharmacokinetic data for the fluoride when considering HF systemic toxicity.

Since the toxicity of HF is largely due to the F^- and the kinetics of the F^- are well defined, if the data from the inhalation study with HF indicates the potential for systemic toxicity at concentrations lower than those that cause nasal effects, a PBPK model of F^- can be developed for extrapolation between species and routes of fluoride administration. The model can then be scaled for humans and validated against the existing literature data on F^- kinetics in humans. The HF Panel further believes that there are sufficient data for HF and soluble fluorides to address many of the endpoints identified by EPA in the proposed rulemaking. In all, the data developed in this proposal will assist EPA in developing an inhalation reference concentration (RfC).

Introduction

EPA proposed a variety of toxicity tests be conducted on hydrogen fluoride (HF) under Section 4 of the Toxic Substances Control Act, including acute and repeated exposure studies, developmental and reproductive toxicity, immunotoxicity and neurotoxicity studies (see 61 Fed. Reg. 38446, July 24, 1996). As part of its proposed test rule on HF and other Hazardous Air Pollutants (HAPs), the Agency has invited the submission of proposals for physiologically-based pharmacokinetic (PBPK) studies to allow for species-to-species and route-to-route extrapolations as a method for satisfying some of the Agency's proposed testing requirements. For the purposes of portal-of-entry effects of inhaled vapors, nasal airflow dynamic models are considered to be physiologically-based models.

HF is a highly reactive, water soluble substance whose deposition and pattern of nasal lesions may be characteristic of a Category I gas. Because of the reactivity of HF and because the major portals of entry into the body will be through the nose and upper respiratory tract, EPA has expressed a potential concern of the effect of HF on the tissues at the portal of entry. Indeed, the regional delivered dose may be an important aspect in the overall risk assessment of HF and calculation of the inhalation reference concentration (RfC).

At the air:tissue interface, HF will interact with tissue components and then enter the body as HF. The reactivity of HF leads to almost complete deposition of HF in the nasal passages, and the hallmark of HF toxicity is likely to be the development of nasal lesions. Given the known chemistry and metabolism of HF, which is outlined below, the HF Panel believes that it is appropriate to use pharmacokinetic data for the fluoride (F^-) when considering HF systemic toxicity. The HF Panel further believes that there are sufficient data for HF and soluble fluorides to address many of the endpoints identified by EPA in the proposed rule making. As discussed below, data indicate that, under physiological conditions, the F^- is the species of interest, regardless of whether the F^- is contributed by HF or by a soluble fluoride, e.g., sodium fluoride. Once absorbed, HF dissociates to the F^-. This dissociation is extremely rapid, and at a physiological pH of 7.4, dissociation of HF to the F^- is strongly favored. Following absorption, the distribution, metabolism and systemic toxicity of the F^- is the same as that following gastrointestinal absorption of a soluble fluoride, e.g., sodium fluoride. Sodium fluoride itself is actually absorbed as HF from the acid environment of the stomach, but rapidly dissociates to the F^-.

Since the toxicity of HF is due to the F^- and the kinetics of the F^- are well defined, a PBPK model of F^- can be developed for extrapolation between species and routes of fluoride administration. The model can then be scaled for humans and validated against the existing literature data on F^- kinetics in humans.

This proposal will:

- address potential portal-of-entry effects due to HF and suggest a means of validating a model for species-to-species extrapolation, i.e., rat to man,

- demonstrate that the chemistry of HF is indistinguishable from other soluble fluorides once absorbed into the body;

- outline the process of developing a PBPK model for HF and soluble fluorides,

- briefly review the available toxicology information on sodium fluoride as a potential surrogate compound to satisfy certain endpoints in the proposed test rule, and

- briefly describe the potential for "delayed effects" from dermal contact with HF.

Hydrogen Fluoride (HF) Pharmacokinetics and Metabolism

Acute, Upper Respiratory Tract Effects of HF

The significant toxicological effects of HF exposure are manifest at the site of contact. Thus, by the inhalation route, significant deposition is predicted to occur in the most anterior regions of the nasal cavity and extending posteriorly to the lower respiratory tract if sufficient exposure concentrations are achieved. Histologically, the lesions induced at the sites of contact with HF are characterized by necrosis with an associated inflammatory response. One day after a single, one hour exposure of rats to HF concentrations of 950 to 2600 ppm, pathologic injury was limited exclusively to the anterior section of the nose (DuPont, 1990). The nasal lesions were characterized by extensive necrosis and squamous metaplasia of respiratory epithelium with inflammation and vascular thrombosis in adjacent submucosal tissues. No compound-related effects were seen in the trachea or lungs. Two or ten minute exposures of rats to 6392 or 1669 ppm, respectively, produced similar effects (Stoneybrook Laboratories, 1996). Lesions of the nasal mucosal membranes of rabbits, guinea pigs, and pigeons exposed for 31 days to HF vapor were reported with a no-effect concentration being established at 3.0 ppm (Ronzani, 1909). Monkeys appeared to be less sensitive to HF compared to rabbits and guinea pigs when exposed to 18.6 ppm, 6-8 hours per day, six days per week for 309 hours (Machle and Kitzmiller, 1935). Humans are reported to have tolerated, with mild nasal irritation (subjective response), 32 ppm for several minutes (Machle et al., 1934). Repeated exposures of humans at concentrations up to 4.7 ppm, six hours per day for 10-50 days, were tolerated without severe effects (Largent, 1960; 1961).

Airway Deposition of HF and Portal-of-Entry Effects

HF is a highly water soluble, reactive vapor. The major portals of entry for HF in humans will be the nose, or upper respiratory tract (URT), and mouth. Morris and Smith (1982) have shown that inspired HF deposits in the nasal cavity with greater than 99.7% efficiency over a concentration range of 40 to 234 ppm when measured in the surgically isolated upper respiratory tract of rats. These data are supported by recent acute inhalation studies (Stoneybrook Laboratories, 1996) in which rats exposed nose-only to 1669 ppm HF or exposed tracheally to 1764 ppm HF for 10 minutes had lesions limited to the initial site of entry (nose for intact rats, trachea for tracheotomized rats). The high URT deposition efficiency and the physicochemical properties of highly water soluble and reactive compounds, like HF, are expected to be Category 1 vapors as described by the U. S. EPA (1994). For Category 1 materials, dose is an important determinant of

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regional response patterns. Regional dose is dependent on airflow patterns which will vary between rodents and humans because of anatomical differences.

Deposition of vapors in the URT is controlled by resistance to gas phase mass transport, i.e. resistance to air phase molecular diffusion, solubility and reactivity in the mucus and tissue, metabolism, and blood flow removal from the tissue (Hanna et al., 1989; Morris, 1990). Since HF dissociates completely in the aqueous milieu of tissues, and is not metabolized, blood flow and metabolic clearance of HF are not expected to be significant factors controlling deposition. Thus, mass transport of HF to the tissue surface, i.e. delivered dose, and factors affecting its transport are likely to be the key determinants of 1) regional lesion distribution in the URT of rats, 2) concentration and exposure duration-dependent distribution of lesions, and 3) interspecies extrapolation of the dosimetry of HF in the URT of rodents and humans.

Recent work in the laboratories of Kimbell et al. (1993) and Hahn et al. (1993) has endeavored to develop computational models of airflow patterns in the rat and human URT. These models have been constructed using finite element modeling techniques such that three dimensional computational fluid dynamics (CFD) simulations of inspiratory airflow can be estimated in rats and humans. These models describe the major airflow patterns through the rat and human nose, taking into account the unique anatomical features of the two species. For example, the rat nasal cavity is elongated. In the rat, air flows in streams that pass over well developed and complicated turbinates with a narrow passageway and small distances between the center of the air stream and the tissue surface. This arrangement presents a highly effective surface area for vapor deposition. The human nasal cavity, in contrast, is more spherical in shape with less complicated nasal turbinates yielding greater distances from the center of the air stream to the tissue lining. Airflow predictions from these models, visualized using three dimensional reconstruction of the nasal cavity surfaces, have been validated against experimental measures of water/dye streams or anemometric measures in models (Kimbell et al., 1993; Hahn et al., 1993).

The rat nasal model has recently been used to predict regions of high flux of formaldehyde vapor to the mucosal surface (Kimbell et al., in press). Like HF, formaldehyde is a highly reactive water soluble gas whose deposition and regional pattern of lesion formation is characteristic of a Category 1 gas. Flux is defined as the rate of movement of mass from the air stream to the surface of the nasal cavity (units of mass/unit time/surface area). These studies with formaldehyde show that the high flux regions correlated well with regions of squamous metaplasia, the toxic response of the nasal epithelium to formaldehyde gas. Therefore, regional flux rates can be correlated with measures of toxic response and used as dose surrogates. Thus, the regional flux corresponding to the NOAEL for high impact sites can be estimated and related to the inspired concentration. Nasal lesions induced by Category 1 vapors are often focal and absent in regions of low flux. An alternative approach to equating a NOAEL to local flux is, therefore, to determine maximal flux values for nasal regions in which there are no lesions. For formaldehyde, the relationship between concentration and regional flux was shown to be linear. Similar regions of high flux in the nasal cavity of humans can be predicted using the human version of the CFD model. In this manner, an exposure level for humans that yield flux values equivalent to the NOAEL flux value in rats can be derived. This approach forms the basis for the proposal below to use the CFD modeling techniques developed for the rat and human URT to determine an RfC for HF.

Approaches to Route-to-Route and Interspecies Extrapolation - Portal of Entry Effects

The available data suggest that the mode of action of HF on tissues, i.e. calcium and magnesium sequestration- and intracellular acidification-induced necrosis, seen in rats is likely to be operative in humans (Anderson and Anderson, 1988). Factors controlling interspecies differences in response are, therefore, confined to dosimetric differences. The proposed approach to developing an RfC for the portal of entry effects of HF is as follows:

- Characterize the concentration- and time-dependent distribution of HF induced nasal lesions;
- Using the Computational Fluid Dynamics (CFD) model of the rat nasal airflow, estimate the HF flux rates for the regions of the nasal cavity that demonstrate lesions at or near the NOAEL (equivalent to the Regional Gas Dose in the EPA RfC methodology);
- Estimate the HF regional deposition patterns in humans using the human CFD nasal airflow model;
- Determine what inspired concentration in humans yields regional flux values equivalent to that predicted with the rat CFD nasal airflow model at or near the NOAEL (equivalent to the Human Equivalent Concentration (HEC) in the EPA RfC methodology); and
- Assess the residual uncertainty in the analysis and derive an inhalation RfC.

The following specific steps are anticipated:

1. Since tissue blocks from the 14- and 90-day inhalation studies (Placke and Griffin, 1991) are no longer available, an inhalation study is proposed. In this study, nasal cavity tissue will be collected according to the method of Mery, et al. (1994), and examined histologically. Interim sacrifices will be included to determine if the potential effects are time and concentration dependent or just concentration dependent.

2. Conduct a detailed mapping of the lesions, including severity scoring, according to the lesion mapping strategy of Mery, et al. (1994). Determine the NOAEL. If necessary, use Benchmark dose methods to estimate the ED_{10} and LED_{10}

3. Develop a rank order of the regions in which lesions appear.

4. Develop the rat CFD model incorporating the HF specific parameters.

5. Correlate the mass flux values to the regions of lesion distribution as in Kimbell et al. (in press) for the various exposure concentrations and duration

6. Implement the human CFD model incorporating the HF specific parameters.

7. Determine the inhalation exposure concentrations and duration that yield equivalent mass flux values determined for the rat at the NOAEL or the maximal flux values for non-affected regions at the LOAEL.

This work will require the assistance of a pathologist well trained in histopathology of the URT, and CFD modeling expertise. The above approach has the advantage of drawing data from nasal tissues and using state-of-the-art computational approaches to interspecies dosimetry estimation.

In addition to the above and as part of the inhalation study with HF, we propose to determine plasma and urinary fluoride levels along with limited histopathology of selected target organs, e.g., heart, spleen, liver, lung and brain. Other tissues would be collected and processed to the block stage for possible future histopathological examination. In the study of Placke and Griffin (1991), no effects on clinical chemical parameters were observed, Thus, these parameters need not be included in the proposed study.

Hydrogen Fluoride Chemistry

It is important to recognize that the toxicity of anhydrous HF occurs in two distinct phases. Phase I is characterized by the destructive action of anhydrous HF on the tissues at the portal of entry, resulting in tissue burns by liquid HF or respiratory distress and injury by HF gas or aerosol. Phase II is characterized by rapid dissociation of HF and the F^- and the systemic transport and disposition of F^- in the body.

Phase I

Anhydrous HF is a strong inorganic acid, a powerful dehydrating agent, and can cause many organic reactions. Anhydrous HF is highly soluble in, and can react with, or catalyze reactions of, oxygen-, nitrogen- and sulfur-containing organic compounds which also are present in biological materials. The dehydrating power and solubility of HF facilitates inter-molecular reactions and catalysis by HF (Simons, 1950) leading to its destruction of body tissues.

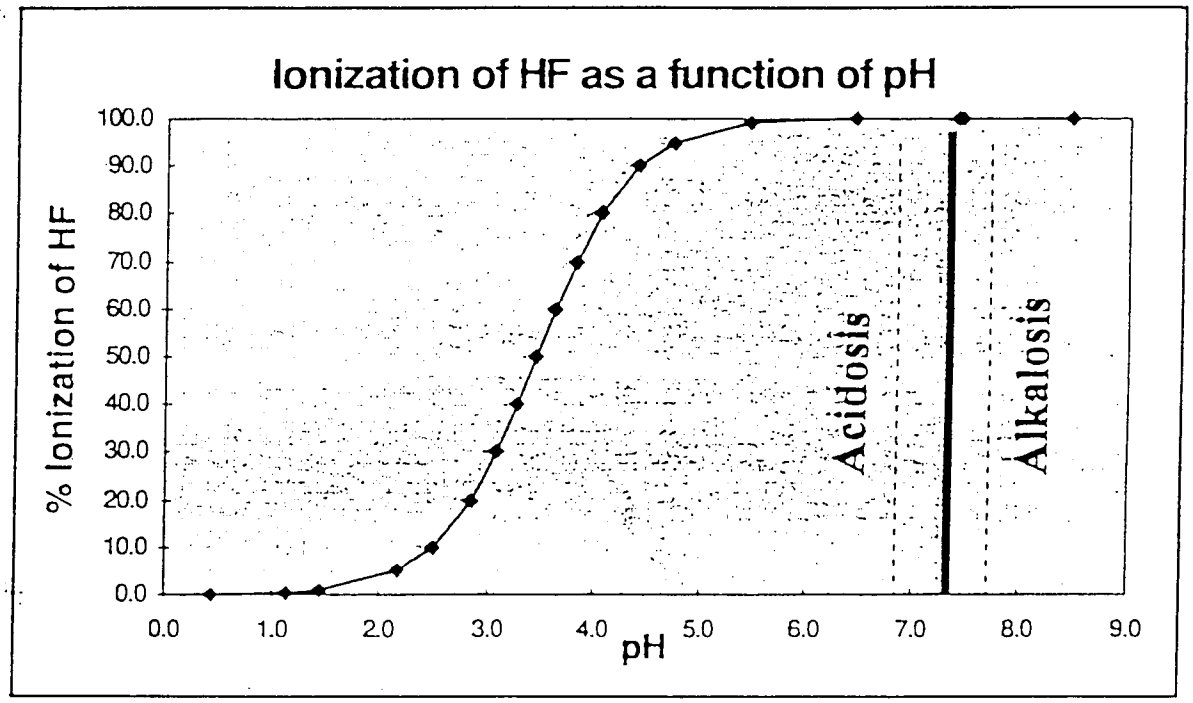
At the site of entry or in contact with moisture in air, anhydrous HF instantaneously and strongly associates with water in the tissues, forming hydrofluoric acid which is a weak acid and may not be fully ionized. It is non-ionic HF, and not F^-, which is more readily transported across cell membranes of all compartments of the body, e.g., from lungs or skin into the blood. For this reason, ingested fluoride is more rapidly absorbed in the stomach (acidic pH) than in the intestines (alkaline pH). It is the concentration gradient of non-ionic HF that is the driving force for HF transport across biomembranes. In transmembrane fluoride transport, non-ionic HF is the primary permeating species (Whitford, 1983; Ekstrand, 1996).

Phase II

The extent of ionization of HF is governed by the Henderson-Hasselbach equation. In pure water solution, HF is partially in molecular form and partially ionized. However, in the extracellular fluid at pH 7.4, HF ($pK_a = 3.45$) is essentially completely ionized ($HF:F^- = 1:9000$). In essence, the HF, as such, does not exist at pH 7.4. Because of the buffering capacity of the body, the 1:9000 ratio is the same whether HF or sodium fluoride (or another soluble fluoride) is introduced into the extracellular fluid. Because of the ionic nature of the reaction, HF will be very

rapidly converted to F^-. This F^- is indistinguishable from F^- derived from sodium fluoride and will have the same physiological distribution and potential toxicity. Figure 1 shows the ionization of HF as a function of pH. Between the extremes of pH which are compatible with life (extreme acidosis, pH - 7.0, and extreme alkalosis, pH = 7.7, Ganong, 1979), HF is essentially completely converted to F^-.

Figure 1



Metabolism and Pharmacokinetics

HF reacts with tissue components of the airway where it is almost completely (>99%) absorbed as HF. As discussed under HF Chemistry and Mode of Action, HF dissociates to H^+ and F^- and primarily exists in the bloodstream, tissues and extracellular spaces as F^-. Protons formed are expected to be buffered by bicarbonate and protein buffers, and regulated by the H^+/Na^+ antiport pumps. Absorbed F^- is not truly metabolized, but exists in the blood as free F^- or binds to calcium and magnesium, forming salts. Free F^- is transported via the blood to all tissues (Perry, et al., 1994). Once in the blood, the F^- behaves in an identical manner to the F^- absorbed from soluble fluoride salts, such as sodium fluoride. Equilibrium with tissues occurs if the exposure is of significant duration (several hours). Deposition occurs in bone where F^- substitutes for hydroxyl groups in hydroxyapatite. Elimination of F^- is primarily through the kidney.

Kinetic Data on Fluoride Ion

Considerable kinetic data are available for F^-. Studies have been performed on the absorption, distribution and excretion of F^- in rats, other species, and in humans. These studies have been thoroughly reviewed by ATSDR (1993). Most of the data was developed for sodium fluoride, which is essentially 100% absorbed following oral administration. Oral absorption is rapid in rats and humans. Fluoride derived from inhalation of HF was shown to be distributed in tissues at concentrations equal to the blood concentration (Morris and Smith, 1982). Repeated high-level exposures can result in deposition of F^- in bones and teeth (Stokinger, 1949), but specific affinity for other tissues has not been shown. Teeth and bone readily take up fluoride following oral exposure. Rates of uptake into bone have been studied in several species. Long-term retention and accumulation of fluoride are primarily confined to calcified tissues in humans. Classical pharmacokinetic models have been developed for F^- in humans, for absorption and deposition, and for bone remodeling. Overall, the data indicate that the pharmacokinetics of F^- are well defined, and can be described with pharmacokinetic models.

Approaches to Route-to-Route and Interspecies Extrapolation - Systemic Effects

If systemic histopathological effects are observed in the inhalation exposure study discussed under Portal-of-Entry Effects, then a pharmacokinetic model is proposed to determine distribution and kinetic constants for absorption and elimination of the F^-. The modeling would be done utilizing the Advanced Continuous Simulation Language (ACSL) model.

Since the potential systemic toxicity of HF is due to the F^-, and the kinetics of F^- are well defined, a pharmacokinetic model could be useful for extrapolation between species and routes of administration. The physiologically-based pharmacokinetic (PBPK) model would be used to estimate the concentration of F^- in blood or other critical tissues of a rat or human exposed to HF at any concentration by the inhalation route.

The data needed to build a PBPK model for HF in rats would be:

- partition coefficients for HF and F^-,
- deposition efficiency of HF in the airways of rats and humans, and
- kinetic data for tissue and plasma F^- after HF inhalation.

Once the kinetic data are developed for HF, an estimation of the kinetic parameters would then be developed for an orally administered fluoride salt, e.g., sodium fluoride. Currently, sufficient kinetic data exist for F^- after oral administration of a fluoride salt in animals and humans (reviewed in ATSDR, 1993). The inhalation study conducted with HF would be utilized to validate the PBPK model. A study utilizing the oral administration of sodium fluoride would be used to confirm the correct estimation of F^- kinetics and distribution. The oral study would include determination of plasma and urinary fluoride concentrations as well as tissue levels and distribution of fluoride.

Finally, a large body of human data exists on F^- kinetics (ATSDR, 1993) after oral administration of sodium fluoride and after HF inhalation exposure. The rat model could be scaled to humans, and validated for humans with the use of human literature data for F^-. Therefore, once the kinetic models for oral and inhalation are established, if needed, many of the endpoints of concern for EPA could then be satisfied by utilizing toxicity data that have been generated for sodium fluoride.

Toxicology Review of Sodium Fluoride

The HF Panel proposes utilizing toxicology data for sodium fluoride to satisfy several of the endpoints cited by EPA in the proposed test rule. Below is a brief review of available toxicity information on sodium fluoride.

Subchronic Toxicity

In the proposed rule, EPA has requested a subchronic study with HF. A 90-day inhalation study has been reported, and is briefly reviewed.

In a 90-day subchronic study (Placke and Griffin, 1991) female and male rats (20/group) were exposed to 0.1, 1.0 or 10 ppm respectively for 6 hours/d, 5 days/week. Observations included clinical signs, body weight, organ weights of liver, kidneys, testes, ovaries, adrenals, heart, spleen, brain and lungs, hematology, blood biochemistry and complete histopathology. Five males and one female rat were found dead during the study in the 10 ppm group. Clinical signs in this group were red-colored discharge from eyes and nose, ruffled fur, alopecia and hunched posture. At 10 ppm, body weights were depressed and in 9 males and 2 females, dental malocclusions were observed. Increases in the number of segmented neutrophils were seen in the high dose male group. Platelets were increased in the high dose males. Mid- and high-dose group males showed decreased numbers of lymphocytes, and RBCs were depressed in high dose males and females. Biochemistry showed decreased serum glucose in the high dose males. Additionally, decreases were seen in serum albumin (high-dose males and females), A/G-ratio (mid-and high-dosed males), and increases were seen in potassium and inorganic phosphorous in both males and females of the high dose groups. Relative organ weights of kidneys, liver, lung, testes, spleen, brain, heart and adrenals were increased at the highest dose. Histopathological changes were not found. The decreases in serum A/G ratio and lymphocytes in the male mid-dose group were too small to have a biological significance and are, therefore, not considered as adverse effects. Thus, the NOAEL in this study was 1.0 ppm.

In addition to the 90-day inhalation study with HF, several subchronic oral toxicity studies have been conducted with sodium fluoride. Many of these studies, however, were conducted prior to implementation of GLPs and were designed primarily to investigate the effect of fluoride administration on tooth development (fluorosis). Thus, these studies were limited in scope and are not considered in this review.

The National Toxicology Program (NTP) conducted repeated oral exposure studies in rats and mice (NTP, 1990). Two-week, 6-month and 2-year studies were conducted in which sodium fluoride was administered via drinking water. Only the 6-month subchronic study will be reviewed.

Male and female F344 rats (n=10/sex/dose group) or B6C3F1 mice (n=8-12/sex/dose group) were administered sodium fluoride in deionized water for 6 months. Rats were administered concentrations of 0, 10, 30, 100 or 300 ppm, and mice were administered concentrations of 0, 10, 50, 100, 200, 300 or 600 ppm. Table 1 shows calculated doses of sodium fluoride administered during the 6-month study. Three control groups were also utilized and consisted of:

- male and female rats and mice provided deionized water and low ($\leq$2.1 ppm) fluoride semi-synthetic diet,
- male and female rats and mice provided sodium chloride supplemented water and low semi-synthetic diet, and
- male and female rats and mice provided deionized water and standard (NIH-07) diet.

Table 1
Calculated Doses of Sodium Fluoride Intake During the 6-Month Drinking Water Study[a]

Sodium Fluoride Concentration (ppm)	0	10	30	50	100	200	300	600
Male Rats[b]	0	0.47	1.4	--	4.7	--	14.0	--
Female Rats	0	0.56	1.7	--	5.6	--	17.0	--
Male Mice	0	1.3	--	6.7	13.3	26.7	40.0	80
Female Mice	0	1.9	--	9.5	19.0	38.1	57.2	114

[a] Doses are in mg sodium fluoride/kg body weight.

[b] Doses were calculated based on the 6-month average body weight and average water consumption (NTP, 1990). Male rats: 430g, 20 mL/day; female rats: 230g, 13 mL/day; male mice: 30 g, 4.0 mL/day; female mice: 21g, 4.0 mL/day.

During the study, the animals were observed twice daily for mortality and morbidity and weighed weekly. Food consumption was determined every other week for the first 13 weeks and then weekly through the remainder of the study. Water consumption was recorded daily. Blood, urine and bone fluoride levels were determined prior to and at termination of the study. At termination, gross examinations were conducted on all animals, and histological examinations were conducted on tissues of rats and mice in the control groups and in rats and mice at the two highest sodium fluoride concentrations.

Food and water consumption were lower in high-dose males and females compared to controls. The fluoride content of bone and urine increased with increasing fluoride concentration in the drinking water. The fluoride content of plasma was significantly increased only in the high-dose groups and in the group of male rats maintained on the standard NIH-07 diet over that of control rats maintained on the low fluoride semisynthetic diet. The principal pathological effect associated with the administration of sodium fluoride for 6 months was observed in the incisor teeth and stomach. Five male rats receiving 300 ppm sodium fluoride had focal or multifocal degeneration of the tooth enamel, primarily in the maturation zone near the apical end of the incisor tooth. In a few animals, small aggregates of enamel-like material were trapped within the cell layers. These changes collectively were diagnosed as dysplasia.

On gross examination, the mucosa of the glandular stomach of most male rats receiving 300 ppm sodium fluoride appeared thickened, and focal or multifocal hemorrhages were observed. Similar but less severe alterations were observed in some rats receiving 100 ppm sodium fluoride. A perforated ulcer of the glandular stomach was seen in a 300 ppm female, and multiple small nonperforated ulcers were seen in one 300 ppm male. Histologically, a subtle focal to diffuse hyperplasia of the mucosal epithelium of the glandular stomach was observed in most male and female rats receiving 300 ppm. This was accompanied by minimal individual cell necrosis (apoptosis) and was most evident in the pyloric region. Nearly all rats receiving 300 ppm sodium fluoride had focal basal cell hyperplasia of the stratified squamous epithelium adjacent to the limiting ridge (junction of the glandular stomach and forestomach). Hyperplasia of the mucosal epithelium of the glandular stomach also was observed in half the males and in two females receiving 100 ppm sodium fluoride, but individual cell necrosis was not. No other histologically significant pathological changes were observed in this study.

Groups of 8 to 12 mice of each sex were administered 0, 10, 50, 100, 200, 300, or 600 ppm sodium fluoride in deionized water *ad libitum* for 26 weeks. The study design was similar to the design utilized for the 6-month study with rats. All but one early death occurred in the high-dose groups: four high-dose males died during weeks 13 and 14; one male mouse in the second highest dose group died during week 19; nine high-dose females died during weeks 8 to 18. All other mice survived to scheduled termination. Among the 13 high-dose animals that died before the scheduled sacrifice, six were killed because they were moribund. Signs of toxicity (thin appearance, hunched posture, weakness) were observed in only two of these before they became moribund. Mice exposed to the four highest doses of sodium fluoride had chalky white teeth. The lower incisors were more affected than upper incisors, and some teeth in mice in the two highest dose groups were

chipped. No other signs of toxicity were observed in any of the animals that died early or that survived to the end of the study.

Body weight gain was depressed in the three highest dose groups for both sexes, and was consistent with the observed decreases in food consumption. Average weekly feed consumption was within 20% of control values for all groups, except high-dose males which consumed only 77% of that consumed by controls. Average weekly water consumption was within approximately 20% of control values for all dosed groups.

The fluoride content of bone and urine was increased in a dose-related fashion with increasing fluoride concentrations in the drinking water. The fluoride concentration in plasma appeared to increase with the dose of fluoride, but the necessity of pooling samples to obtain sufficient material for analysis prevented performance of meaningful statistical analyses of these data. A number of histological alterations were identified in mice dying early or sacrificed while moribund and consisted primarily of acute nephrosis, the likely cause of death in these mice.

Compound-related effects were observed in the femur and, to a lesser extent, in the tibia of nearly all male and female mice receiving 100 to 600 ppm sodium fluoride and 5/10 males receiving 50 ppm. In mice receiving 600 ppm some lamellae appeared thicker and more irregular with cement lines that were less prominent and smooth in contour. The osteoid seams lining some osteons (haversian canals) of the cortical bone were increased in thickness. These changes were not uniform or diffuse. In mice receiving 50 or 100 ppm only occasional prominent osteoid seams were evident. Lesions of the lower incisors were generally more extensive in the mice receiving 300 or 600 ppm than in mice receiving lower doses. The enamel from the affected mice that were examined had focal or multifocal irregularity of the layer of ameloblasts, with projections and folds that sometimes surrounded isolated islands of enamel. In some mice, there was loss of the surface columnar cells and variable loss of cells from the stratum intermedium. The remaining cells were reduced in size and disorganized. These changes collectively were diagnosed as dysplasia.

Developmental Toxicity

No specific studies on the developmental toxicity of HF have been reported. For sodium fluoride, developmental toxicity studies have been reported for rats and rabbits in which the compound was administered via drinking water (Collins, et al., 1995; Heindel, et al., 1996).

In the study of Collins et al. (1995), pregnant rats (n=35-37/group) were administered 0, 10, 25, 100, 175 or 250 ppm sodium fluoride in drinking water throughout gestation. On a mg sodium fluoride/kg body weight basis, the dose levels were 0, 1.4, 3.9, 15.6, 24.7 and 25.1 mg/kg. Reduced food and water consumption and body weights were observed in the 175 and 250 ppm groups, and was considered due to poor palatability of sodium fluoride at these concentrations. No effects on reproductive outcome, and no biologically significant developmental effects were observed in this study. A decrease in the mean number of implants per litter was observed in the 250 ppm group, and is related to a decline in the number of corpora lutea. A statistically significant increase in the number of fetuses with three or more skeletal variations was observed in offspring of dams administered 250 ppm sodium fluoride. However, the number of litters containing fetuses with

three or more skeletal variation was not statistically increased. Thus, sodium fluoride was not teratogenic.

In a study reported by Heindel, et al. (1996), pregnant rats (n= 26/group) were administered 0, 50, 150 or 300 ppm sodium fluoride in deionized drinking water during days 6-15 of gestation; dose levels were 6.6, 18.3, or 27.1 mg of sodium fluoride/kg body weight. Also, pregnant rabbits (n= 26/group) were administered 0, 100, 200 or 400 ppm sodium fluoride in deionized drinking water during days 6-19 of gestation; dose levels were 10.3, 18.1 or 29.2 mg sodium fluoride/kg body weight. Declines in body weights and food consumption were observed in the high dose groups for both rats and rabbits, and were attributed to decreases in water consumption due to poor palatability of sodium fluoride in drinking water. No effects on reproductive outcome (implantations, corpora lutea, etc.) were observed in either species. Also, no effects on fetal body weights or developmental malformations were observed in either species.

As part of this study, these investigators collected serum during gestation and measured total fluoride levels (Table 1). As can be seen in the table, oral administration of sodium fluoride at concentrations of up to 400 ppm in rabbits resulted in blood fluoride levels of 0.7 mg/mL. Further, the data suggest that oral absorption in the rabbit at about comparable doses, in mg F/kg body weight, is about an order of magnitude greater in rabbits than rats.

In summary, these studies reveal that sodium fluoride does not induce developmental toxicity at levels up to 400 ppm (29.2 mg sodium fluoride/kg body weight) in drinking water.

Table 2[a]
Comparison of Sodium Fluoride Comparison in Drinking Water, Dosage Equivalents, and Serum Levels for Rats and Rabbits

	Rats				Rabbits			
Nominal concentrations in drinking water (ppm)	<0.6	50	150	300	<0.6	100	200	400
Calculated dose from drinking water mg NaF/kg body weight/day[b]	--	6.6	18.3	27.1	--	10.03	18.1	29.2
Calculated dose from food[c] mg NaF/kg body weight/day	2.21	2.17	2.19	2.12	1.72	1.86	1.77	1.48
Calculated total dose from food and water mg NaF/kg body weight/day[d]	2.21	8.78	20.53	29.20	1.72	12.70	19.43	30.33
Maternal serum concentration[e] F (µg/mL)	0.007	0.035	0.039	0.187	0.06	0.24	0.39	0.70

[a] Adopted from Heindel, et al. (1996).

[b] Calculated intake of NaF was based on the measurement of maternal relative water consumption (g/kg body weight/day) and the nominal concentration of NaF added to the drinking water for each experimental group. Control drinking water was below the method detection limit of 0.6 ppm NaF.

[c] NIH-07 rodent chow contained 11.6-13.4 ppm F (Average =12.4 ppm F, equivalent to 27.41 ppm F, equivalent to 27.41 ppm NaF). Purina rabbit chow contained 14.6-16.6 ppm F (average = 15.6 ppm F, equivalent to 34.48 ppm NaF).

[d] Calculated intake of fluoride or of NaF equivalents was used on measurement of maternal relative food consumption g/kg body weight/day) during the treatment period, as well as average concentration of fluoride in NIH-07 rodent chow or Purina rabbit chow.

[e] Maternal serum concentrations of fluoride were determined on GD 16 (rats) or GD 20 (rabbits).

Reproductive Toxicity

No specific reproductive toxicity data on HF are available. The effect of sodium fluoride on fertility has been studied in mice, rats and rabbits (Araibi, et al., 1989; Chinoy, et al., 1991 Chinoy and Sequeira, 1989; Chinoy and Narayana, 1994). Fluoride, administered by gavage or through the diet, reduced male fertility and caused histological changes in sperm cells at oral doses of about 5 mg sodium fluoride/kg body weight. However, intratesticular injection of sodium fluoride (Sprando, et al., 1996) at doses of 0, 50, 175 or 200 ppm produced no changes in sperm morphology or spermatogenesis; dose equivalents were 0, 0.011, 0.037 and 0.042 mg sodium fluoride/kg body weight, respectively.

In a 2-generation reproduction study, female mice received 0, 110, 220, 440 mg/L sodium fluoride in their drinking water and were mated with untreated males. In the control group, a progressive decline in litter production with successive litters occurred in both generations. By 6 weeks of treatment, about 50% of the females in the highest dose group had died and by week 17 of exposure all females in this group had died. Also, in the 110 mg/L dose group only nine litters were born over a 10 week period. This study is considered to be of limited design (Messers, et al., 1973).

In a 3-generation study, female mice of the first generation were orally exposed to 0 or 2 mg F/kg as NaF, equivalent to 0 and 0.3 mg F/kg body weight /day, respectively, and mated with untreated males (Tao, and Suttie, 1976). The second and third generation females received 0, 2 and 100 mg F/kg diet. Relevant observations included among others, growth, reproductive response, litter size, pup weight and incidence of stillbirth. No compound-related effects on these parameters were observed. The protocol of this study is considered incomplete and kidney infection may have disturbed the sensitivity of the test.

In an unpublished two-generation reproduction study (cited in Sprando, et al., 1996), rats were administered 0, 25, 100, 175 or 250 ppm sodium fluoride in drinking water for approximately 14 weeks (10 weeks of pretreatment, 3 weeks of mating and 1 week of post-weaning). No significant reproductive differences between treated or control animals were reported, and no effects on sperm count, testis weight, testicular pathology or hormonal parameters (LH, FSH or testosterone) were indicated. However, the full report was not available for critical review.

Although decreases in fertility were observed in mice administered sodium fluoride by gavage or through the diet, other studies conducted under more rigorous conditions and at higher doses, on a mg sodium fluoride/kg body weight basis, indicate that this material is not a reproductive toxicant.

Neurotoxicity

Neurobiological studies have suggested a variety of basic mechanisms by which F^- can affect the function of the nervous system. Although these studies do not specifically address the issue of neurotoxicity, they do establish the F^- concentration range that is required for biological impact on the nervous system and elucidate the function of F^- which is a normal constituent of cerebrospinal fluid. Kay et al. (1986) found that F^- can beneficially stabilize the operation of voltage-dependent

calcium (Ca++) channels in neurophysiological experiments. Jope and Lally (1988) demonstrated that 12 mM F^- was required to stimulate Ca++ influx in synaptosomes. The enhanced Ca++ influx was ATP-independent. There are a number of possible mechanisms for this effect, but Jope and Lally (1988) favor the hypothesis that F^- directly activates a guanine nucleotide binding protein associated with receptor-gated Ca++ channels.

Increased intracellular concentration of unbound Ca++ can influence a number of basic neuronal processes including protein phosphorylation, activation of proteases, neurotransmitter release, and perhaps neuronal growth. Nakagawa-yagi et al. (1993), for example, studied the growth of cells maintained *in vitro* and found that F^- could inhibit neurite outgrowth. This inhibitory effect was blocked by Mn++ which is a non-specific blocker of Ca++ entry. The effect of F^- on neurite growth is therefore probably mediated by its ability to increase intracellular Ca++. In summary, the available neurobiological data points to the ability of F^- to affect neuronal functions by its influence on Ca++ flux across neuronal membranes.

Since fluoride has the ability to affect a key neurobiological process such as Ca++ flux, it is perhaps not surprising that relatively high exposure concentrations of sodium fluoride *in vivo* have been reported to alter behavior of rats. The behavioral effects, however, are quite subtle. Mullenix et al. (1995) studied the effects of 100 ppm of sodium fluoride in drinking water for six weeks in male and female rats. The amount of sodium fluoride that can be administered subchronically is limited by the high incidence of death associated with dehydration that is apparent with 175 ppm exposures. The authors conducted a detailed analysis of the number of initiated behaviors, the total duration of specific behaviors, the temporal distribution, i.e., whether behaviors were clustered or dispersed in time, of specific behaviors, and the temporal distribution for sequences of different types of behavior. The analysis involved over 100 dependent variables for each rat for each category of initiations, duration, and temporal distribution. Whereas the male rats were not affected, females showed several statistically significant differences relative to control. Sodium fluoride treated females had fewer initiations of sitting behavior, grooming-attention sequences, grooming-exploration sequences, and there was increased temporal clustering of grooming-attention sequences. The vast majority of the hundreds of other measures were apparently not significantly affected.

Similar behavioral changes were noted in rats that were exposed during gestation or neonatally, and despite a few differences, the effects and their magnitude were not markedly different from adult exposures. The developmental studies did provide important additional information in that 75 ppm was identified as an exposure concentration without identifiable behavioral effects. Potential concern about developmental exposures should therefore be similar to the level of concern that might be associated with adult exposures. Unfortunately, the extent of concern is difficult to judge because it is unclear how to interpret the toxicological importance of the effects described by Mullenix et al. (1995). Changes in the temporal clustering of a specific behavioral sequences such as grooming followed by paying attention to a location in the cage, for example, is not obviously maladaptive for the rat and is not considered significant.

The behavioral measurements in the Mullinex et al. (1995) study are far more complex than the simple parameters that comprise the functional observational battery and motor activity

assessments in regulatory neurotoxicology studies. Protocols conducted under applicable EPA neurotoxicology test guidelines can detect gross phenomena such as tremors and ataxia or substantial (30-40%) increases and decreases in the amount of motor activity. The behavioral changes described by Mullinex et al. (1995), however, are simply too subtle to be among the kinds of effects that a standard neurotoxicology study has the precision to measure. It is furthermore unlikely that the neuropathological evaluation conducted under guideline tests would reveal any structural anomalies that were not detected during a standard 90-day toxicology study (Placke and Griffin, 1991) which included microscopic evaluation of brain tissue by standard pathological methods.

Conducting EPA guideline neurotoxicology tests is not necessary because such studies would not increase the ability of the EPA to identify and assess any risk that might be associated with exposure to fluoride. The request for standard neurotoxicology studies should be deleted from the testing requirements for the reason that such studies would not improve the quality of information that is already available.

Immunotoxicity

Although there are no specific studies to evaluate the immunotoxicity of inorganic fluorides, there are data from repeated dose studies in animals with HF and inorganic fluorides and from epidemiological studies of communities with fluoridated water supplies indicating that fluorides do not produce immunotoxic effects.

Rats were exposed to hydrogen fluoride at 0, 0.1, 1.0 or 10 ppm for 91 days (Placke and Griffin, 1991; see Subchronic Toxicity Section). No histopathological effects were reported in the spleen, thymus or bone marrow. The slight changes in several hematological parameters, e.g. decreased lymphocytes, increased what blood cell counts, were judged by the study authors as having minimal toxicological significance, and these effects were probably secondary to the decreased food consumption and the dental malocclusion noted in the animals.

Considering the numerous epidemiology studies that have been conducted in communities with fluoridated water supplies, it is unlikely that immunosuppression, and a consequent increased sensitivity to infection or other disease, could be associated with fluoride exposures. In addition, the American Academy of Allergy concluded that there are no suggestions of any immune reactions occurred with oral exposure to fluoride (cited in ATSDR, 1993).

At least four chronic bioassays have been conducted with sodium fluoride. Mice were exposed to sodium fluoride in their drinking water for two years to 25, 100 or 175 mg/L, or in their feed to 4, 10 and 25 mg/kg/day. Hematological and histopathological examinations did not suggest any immunological involvement in these studies. A similar lack of immunological involvement was noted in two chronic rat studies with dose levels up to 4.29 mg F/kg/day in a drinking water study, and 11.24 mg F/kg/day in a feeding study (NTP, 1990; Maurer, et al. 1990, Maurer, et al. 1993). In the NTP drinking water studies with rats and mice, histopathological evaluation included mandibular and mesenteric lymph nodes, bone marrow, spleen and thymus at 24 and 66 weeks, and at study termination at 105 weeks. Hematology measures, performed at 24 and 66 weeks in rats and

at 24 and 66 weeks in mice, included white blood cell count with differentials and platelet counts. No toxicologically significant findings were observed in these studies.

There are two major consequences associated with immunosuppression in animals or man. The most common is an increased susceptibility to infections by bacteria, viruses, fungi and parasites. As less frequent complication is an increased incidence of cancer.

Numerous epidemiology studies have examined the relationship between fluoridated water and cancer (reviewed in ATSDR, 1993). The weight of the evidence strongly suggests that no relationship exists. One of the most recent and thorough studies examined >2,300,000 cancer deaths and >125,000 cancer cases in U.S. counties exposed to artificially fluoridated drinking water for up to 35 years (Hoover, et al., 1991, as cited in ATSDR, 1993). No relationship between cancer incidence or mortality and duration of fluoridation was found. In addition, one study reported an inverse relationship between fluoride levels and cancer of the oral cavity and pharynx for populations in Norway (ATSDR, 1993).

In conclusion, data from numerous epidemiology studies of populations exposed to fluoridated drinking water, extensive histopathological and hematological examinations from four lifetime dosing studies with sodium fluoride in rats and mice and a 90-day inhalation study with HF in rats, do not show an association with increased susceptibility to infection, increased mortality or carcinogenicity and do not suggest that fluorides are immunotoxic.

"Delayed" Effects of HF

EPA had expressed concern that the HF molecule causes toxicity in a manner different from the dissociation of HF into H ions (H) and F ions (F^-). Recently, EPA representatives stated that they had become aware of a report that dermal exposure to HF resulted in "delayed" effects. The specific source of the report or literature citation was unknown. It was EPA's belief, however, that the occurrence of delayed effects appeared to support the idea that the HF molecule was the cause of toxicity, rather than the fluoride $^-$ derived from the dissociation of HF.

Delayed effects from dermal exposure to HF are well recognized. Dibbell (1970) referenced a classification of hydrofluoric acid burns proposed by the Division of Industrial Hygiene of the National Institutes of Health (NIH, 1943). For hydrofluoric acid concentrations of 0 to 20%, the NIH stated that the "burn manifests itself by pain and erythema as late as 24 hours after the burn".

Anderson and Anderson (1988) have summarized the manner in which HF manifests its dermal effects:

> HF has "... an ability to penetrate the intact skin and subdermal tissues, where it dissociates into its ionic form, F^- (Gutknecht, 1981; Craig, 1964). ... As fluoride ions penetrate, they cause an unusually characteristic persistent and intense pain. Klauder, et al. (1955) has attributed this 'excruciating pain' to the reactivity of the dissociated fluoride with tissue calcium ions (Ca^{++}). This causes gradual depletion of tissue calcium in the affected area that results in cellular release of potassium ions from the local nerve endings and intense nerve

stimulation. The latent period before the burn becomes evident is dependent on the concentration and temperature of the acid, the length of time it has been in contact with the skin, and the rate of precipitation of Ca^{++} (Browne, 1974; Derelanko, et al. 1985)".

The precipitation of calcium is the likely mechanism for the delayed effects and ultimate elicitation of pain associated with dilute HF skin exposure. This mechanism has been given credence by treating such exposures with intra-arterial calcium salts. Vance (1986) reported success in treating ten individuals, with hand or finger exposure to HF in concentrations ranging from 12% to 50%, who had an onset of symptoms ranging from two to eight hours after exposure. The intravenous infusion of a calcium gluconate solution was very effective in relieving the pain and limiting or preventing tissue injury.

Conclusions

In summary, we have provided information indicating that:

- The portal-of-entry effects observed following inhalation exposure can be utilized to validate regional flux estimates generated from computerized models of rat nasal airflow. Similar models of human regional flux can be utilized to estimate regional flux values for the human nasal cavity. Rat and human HF concentration-dependent flux values form the basis for deriving a state-of-the-art RfC for HF.

- The chemistry and toxicity of HF are indistinguishable from other soluble fluorides once absorbed into the body.

- It is the undissociated form of HF which is transported across biological membranes. However, once transported and at physiological pH, HF rapidly dissociates to the F^- and the H^+ is almost completely neutralized. The reaction kinetics ratio is 1:9000 ($HF:F^-$).

- A PBPK model can be constructed from existing data. The PBPK model would be developed if systemic effects are observed from the inhalation study conducted for the portal-of-entry effects study. The PBPK model for would be validated with the inhalation study with HF and an oral study with sodium fluoride. Finally, the model would then be scaled to humans.

The HF Panel looks forward to having an open and productive dialogue with EPA regarding the HF testing that the Agency has proposed. As a first step in that dialogue, the HF Panel has described the chemical and pharmacokinetic reasons why extensive testing of HF for systemic effects is both impractical, because of the difficulty in working with HF, and unnecessary, because of the rapid dissociation of HF to the F^- in biological systems. The HF Panel has determined that PBPK modeling provides an avenue for developing the type of toxicity data that EPA is interested in accumulating for HF. The HF Panel looks forward to receiving the EPA's feedback on this proposal.

Acknowledgements:

The following scientists particpated in the preparation of this proposal:

Dr. William J. Brock, Co-Chair, HF Medical and Toxicology Task Group, DuPont

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APPENDIX III

EPA JUNE 26, 1997, RESPONSE TO ALTERNATIVE TESTING PROPOSAL

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 26 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Elizabeth Festa Watson
Manager, Hydrogen Fluoride Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Watson:

EPA has reviewed the alternative testing proposal for hydrogen fluoride (HF) entitled "Proposal for a Physiologically-Based Pharmacokinetics (PBPK) Model for Hydrogen Fluoride," dated November 22, 1996, and submitted by CMA on behalf of the Hydrogen Fluoride Panel.

This proposal was prepared in response to EPA's invitation for proposals for pharmacokinetics (PK) studies for the hazardous air pollutants (HAPs) listed in the proposed test rule for HAPs (61 FR 33178; June 26, 1996). The PK studies would be used to inform the Agency about route-to-route extrapolation of toxicity data from routes other than inhalation when it is scientifically defensible in order to empirically derive the inhalation risk. The PK proposals could form the basis for negotiation of enforceable consent agreements (ECAs) that would provide for testing in lieu of some or all of the tests proposed in the HAPs rule.

The following provides a background to EPA's method of evaluating the proposed PK strategies. As you recall, in the preamble to the proposed test rule, EPA indicated that, when reviewing PK proposals, it would use the Gerrity and Henry (1990) decision tree as an element in evaluating the proposed PK studies. The Agency also indicated that it would use mechanistic data in determining the appropriateness of route-to-route extrapolation of the existing data base as an alternative to conducting some or all of the testing required under the proposed HAPs test rule. Pharmacokinetics and mechanistic data may be used to inform the Agency about route-to-route extrapolation when EPA determines that extrapolation from existing studies may provide sufficient data to substitute for required testing under the proposed rule. Pharmacokinetics and mechanistic data alone may not be used to substitute for proposed required testing when studies by a route other than inhalation do not exist or are deemed by EPA to be inadequate. In such cases, however, pharmacokinetics and mechanistic data may be used to support a decision that required testing could be conducted using routes other than inhalation.

EPA has concluded that this proposed strategy offers sufficient technical merit to warrant further consideration. The Agency invites the Hydrogen Fluoride Panel to consider EPA's preliminary technical analysis of the proposal, a copy of which is enclosed in this letter. Please note that this analysis, including all discussions concerning data adequacy and test procedures/methods pertain only to the adequacy of the PK proposal for its intended purpose and not to the statutory basis for issuing the HAPs rule under section 4 of the Toxic Substances Control Act (TSCA).

If, after the Panel has had the opportunity to review this analysis, you have a continued interest in pursuing the ECA process as an activity distinct from the test rule process, please respond to me in writing by July 31, 1997. Depending on the Panel's response, EPA will determine whether or not to proceed with the ECA process. (The procedures for ECA negotiations are described at 40 CFR 790.22(b).) Under this process, EPA would publish a notice in the Federal Register soliciting interested parties to participate in or monitor negotiations for an ECA on hydrogen fluoride. The notice will also announce a date for a public meeting to negotiate the ECA. At these negotiations EPA may raise issues, based on the Agency's further review of the proposed strategy, that differ from those contained in the preliminary technical analysis. EPA notes that, as a result of unexpected complexities arising in the review of the PK proposals and contrary to the statement in the preamble to the proposed HAPs test rule, the Agency will not be able to conclude ECAs within 12 months of the date of the HAPs proposal.

The document submitted by the Hydrogen Fluoride Panel went beyond PK by including an alternate testing strategy to respond to the testing identified in the proposed HAPs test rule. EPA's evaluation of this proposal identifies changes or additions that provide for testing of hydrogen fluoride as an alternative to the testing contained in the proposed HAPs test rule. If this testing is incorporated into an ECA that is successfully concluded between EPA and the Panel, and if the data resulting from testing under the ECA are acceptable to the Agency, such testing will provide an alternative to some or all of the testing proposed for this substance in the HAPs test rule. If testing under the ECA does not fulfill the Agency's needs, EPA reserves the right to meet these needs through rulemaking.

EPA notes that the Hydrogen Fluoride Panel makes certain assumptions regarding the interpretation and use of the available toxicological database for hydrogen fluoride and the proposed surrogate test substance, sodium fluoride (NaF). The testing requirements for HF in the proposed HAPs test rule were identified by EPA for the purpose of providing a database to permit the assessment of residual risk following the implementation of the maximum achievable control technology (MACT) standards required by the Clean Air Act. EPA must apply rigorous standards to determine the adequacy of studies to be used for route-to-route extrapolation. Although, as stated earlier in this letter, EPA considers its current analysis of the NaF studies to be preliminary, the Agency will be prepared to discuss all issues in detail with the Hydrogen Fluoride Panel if the Agency decides to proceed with the ECA process.

It is important that member companies of the Hydrogen Fluoride Panel recognize the importance of responding to the request for comments on the proposed HAPs rule. The submission of a PK proposal to develop an ECA to conduct testing alternative to that contained in the HAPs test rule is no guarantee that EPA and the Panel will, in fact, conclude such an agreement. Therefore, I urge the companies to submit comments on the proposed HAPs rule as an activity separate from the ECA process. Please submit three copies of written comments on the proposed HAPs test rule, identified by document control number (OPPTS-42187A; FRL-4869-1) to: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Document Control Office (7407), Rm. G-099, 401 M St., SW, Washington, DC 20460.

In sum, EPA would like to thank the Hydrogen Fluoride Panel for your creative and thoughtful initial proposal. If you have any technical questions about EPA's comments on your proposal, please contact Annie Jarabek at (919) 541-4847 (voice), (919) 541-1818 (fax), or jarabek.annie@epamail.epa.gov (e-mail). For questions about the ECA process, please contact Richard Leukroth at (202) 260-0321 (voice), (202) 260-8850 (fax), or leukroth.rich@epamail.epa.gov (email).

Sincerely,

Charles M. Auer
Director
Chemical Control Division

Enclosure

Preliminary EPA Technical Analysis of Proposed Industry Pharmacokinetics (PK) Strategy for Hydrogen Fluoride

June, 1997

Chemical Name:	Hydrogen Fluoride		
CAS No.:	7664-39-3	**Molecular Weight:**	20.01
Vapor Pressure:	760 torr at 20 °C	**Chemical Formula:**	HF
PK Proposal Submitted by:	The Chemical Manufacturers Association's Hydrogen Fluoride (HF) Panel, dated November 22, 1996, and entitled "Proposal for a Physiologically-Based Pharmacokinetics (PBPK) Model for Hydrogen Fluoride".		

Preliminary EPA Technical Analysis of Proposed Industry Pharmacokinetics (PK) Strategy for Hydrogen Fluoride

(1) Introduction

EPA is providing the following preliminary technical analysis and suggestions in response to a proposal by the Hydrogen Fluoride Panel for conducting pharmacokinetics (PK) studies and additional toxicity testing. This proposal was prepared in response to EPA's invitation for proposals for pharmacokinetics (PK) studies for the hazardous air pollutants (HAPs) listed in the proposed test rule for HAPs (61 FR 33178; June 26, 1996). The PK studies would be used to inform the Agency about route-to-route extrapolation of toxicity data from routes other than inhalation when it is scientifically defensible in order to empirically derive the inhalation risk. The PK proposals could form the basis for negotiation of enforceable consent agreements (ECAs) that would provide for testing in lieu of some or all of the tests proposed in the HAPs rule. (The procedures for ECA negotiations are described at 40 CFR 790.22(b).) Accordingly, this analysis, including all discussions concerning data adequacy and test procedures/methods pertains only to the adequacy of PK proposal for its intended purpose and not to the statutory basis for issuing the HAPs rule under section 4 of the Toxic Substances Control Act (TSCA).

Pharmacokinetics and mechanistic data may be used to inform the Agency about route-to-route extrapolation when EPA determines that extrapolation from existing studies may provide sufficient data to substitute for required testing under the proposed rule. Pharmacokinetics and mechanistic data alone may not be used to substitute for proposed required testing where studies by a route other than inhalation do not exist or are deemed by EPA to be inadequate. In such cases, however, pharmacokinetics and mechanistic data may be used to support a decision that required testing could be conducted using routes other than inhalation.

EPA acknowledges that if an ECA is successfully concluded between the Agency and the Panel that provides for PK studies and other testing and if the data resulting from testing under the ECA are acceptable to the Agency, such testing will provide an alternative to some or all of the testing proposed for this substance in the HAPs test rule. If testing under the ECA does not fulfill the Agency's needs, EPA reserves the right to meet these needs through rulemaking.

(2) Toxicokinetic Properties

Hydrogen fluoride (HF) is very soluble in water and in most organic compounds. Toxicity of anhydrous HF occurs in two distinct phases. Phase I is characterized by the destructive action of anhydrous HF at the portal-of-entry. HF instantaneously and strongly associates with water in the tissues forming hydrofluoric acid which is a weak acid and may not be fully ionized. Phase II is characterized by rapid dissociation of HF and the F^- with systemic transport and disposition

of F^- in the body. The extent of ionization of HF could be estimated by the Henderson-Hasselbach equation. In pure water solution, HF is partially in molecular form and partially ionized. In the extracellular fluid at pH 7.4, however, HF (pK_a = 3.45) is expected to be completely ionized according to the Henderson-Hasselbach equation ($HF:F^-$ = 1:9000).

HF reacts with tissue components of the respiratory tract where it is almost completely (> 99%) absorbed as HF. Morris and Smith (1982) have shown that unidirectional exposure results in an HF deposition of greater than 99.7% efficiency in the nasal cavity of rats over a concentration range of 40 to 234 ppm. Since HF dissociates completely in the aqueous milieu of tissues, and is not metabolized, blood flow and metabolic clearance of HF are not expected to be significant factors controlling deposition. EPA agrees that the high deposition efficiency in the upper respiratory tract (URT) and the physicochemical characteristics of high water solubility and reactivity support designation of HF as a Category 1 gas (U.S. EPA, 1994). Additional mode-of-action information suggests that circulating F^- due to dissociation of the parent compound may raise concern for remote (systemic) effects. Dosimetry models for Category 1 gases require detailed description of determinants governing uptake in the respiratory tract.

The mode of action of HF on tissues is suggested to be calcium and magnesium sequestration and necrosis induced by intracellular acidification. Thus, species differences are proposed as likely to be dosimetric and not pharmacodynamic.

Free F^- is transported via the blood to all tissues or binds to calcium and magnesium forming salts. Deposition occurs in bone where F^- substitutes for hydroxyl groups in hydroxyapatite. Elimination of F^- is primarily through the kidney. Long-term retention and accumulation of fluoride are primarily confined to calcified tissues in humans. Epidemiological study by Derryberry et al. (1963) is interpreted as indicating that a threshold for minimal increases (Grade I) in bone density caused by fluoride (fluorosis) is below 3.38 mg/m^3 of fluoride (4.3 ppm HF). Grade I fluorosis results in no medically recognized dysfunction. The Threshold Limit Value (TLV) committee considers HF as a primary irritant so that a TLV-Ceiling is recommended at 3 ppm (2.6 mg/m^3) (ACGIH, 1992).

(3) Proposed Hydrogen Fluoride PK Strategy

This section describes the key aspects of the proposed PK strategy entitled "Proposal for a Physiologically-Based Pharmacokinetics (PBPK) Model for Hydrogen Fluoride" submitted by the Hydrogen Fluoride Panel.

The HF Panel proposed to develop an airflow model of the URT mass flux in the rat and to validate the model by mapping the distribution of lesions observed in a study of unspecified duration. The HP Panel proposed to perform interspecies extrapolation based on computational fluid dynamics (CFD) modeling of mass flux in rats and humans as currently developed for formaldehyde. Plasma and urinary F^- levels would be determined as part of the inhalation study.

If remote (systemic) histopathology were observed in this study, then the HF Panel proposed to develop a systemic model of F^- disposition and to validate it with available laboratory animal and human kinetic information from studies using sodium fluoride (NaF) as a surrogate for HF. The HF Panel also proposed to develop the model for remote compartment distribution on the basis of data on NaF asserting that the buffering capacity of the body (i.e., the HF:F^- ratio of 1:9000) is the same whether HF or another soluble fluoride such as sodium fluoride (NaF) is introduced into the extracellular fluid. The HF Panel asserted that F^- from HF is indistinguishable from F^- derived from NaF and will have the same physiological distribution and potential toxicity. Thus, the Panel proposed to use the PBPK model with the remote compartment structures to extrapolate existing NaF oral data on required systemic endpoints. The behavioral effects at 100 ppm NaF in drinking water for 6 weeks in male and female rats observed by Mullenix et al. (1995) were proposed to address the neurotoxicity data need. The data of Collins et al. (1995) and Heindel et al. (1996) on the developmental effects of NaF in drinking water were proposed to fulfill this data need. The oral data base on NaF was proposed to fulfill the data need for reproductive toxicity: Messers et al. (1973) is a 2-generation reproductive study in mice; Tao and Suttie (1976) is a 3-generation study in mice; and a 2-generation study in rats cited in Sprando et al. (1996). No immunotoxicity testing was proposed; the epidemiologic data and the lack of histopathology on a previous 90-day study (Placke and Griffin, 1991) were cited as evidence for lack of concern for potential immunotoxicity.

Table 1 compares the testing provisions described in the proposed HAPs test rule with the PK proposal submitted by the Chemical Manufacturers Association's Hydrogen Fluoride (HF) Panel. This table also summarizes EPA's preliminary response to the Panel's PK proposal. Detailed discussion of EPA's preliminary technical analysis are presented in section 4 of this preliminary technical analysis.

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TABLE 1. Summary Comparing Proposed Testing Provisions for HF

Testing	Acute	Subchron	Neuro (A & SC)	Develop	Repro	Immuno Screen
Proposed HAPs Rule	X	X	X	X	X	X
HF Panel PK Proposal	New[a]	X[b]	R-NaF[c]	R-NaF[d]	R-NaF[e]	-[f]
Preliminary EPA Response to PK Proposal	-[1]	X[2]	X (R)[3]	R-NaF[4]	R-NaF[5]	X[6]

X Testing requirement in the proposed HAPs test rule
R Route-to-route extrapolation

Acute testing:

New[a] New data (Stonybrook, 1996) and a previous acute study (DuPont, 1990) proposed to fulfill this data need. Stonybrook (1996) study included bronchoalveolar lavage (BAL). No macrophage function addressed. Alarie respiratory sensory irritation test not proposed.

-[1] EPA believes at this time that this data need is adequately addressed by the new Stonybrook (1996) data with the exception of the macrophage function assay. EPA maintains that the macrophage function assay as required in the proposed HAPs test rule is needed and could be performed as a satellite to other proposed inhalation testing.

Subchronic testing:

X[b] The HF Panel proposed an inhalation study with the duration not explicitly specified. Interim sacrifices proposed to determine whether C, t, or (C x t) product determines toxicity. Detailed lesion mapping (Mery et al., 1994) proposed to correlate with mass flux from Kimbell et al (in press).

X[2] EPA can accept the proposed inhalation study with limited histopathology, under an acceptable ECA, given the determination of plasma and urinary fluoride levels. EPA believes that this subchronic study should be 90 days in duration to comply with EPA guidelines for subchronic studies.

Neurotoxicity testing (A & SC):

R-NaF[c] Route-to-route extrapolation of behavioral effects of 100 ppm sodium fluoride (NaF) in drinking water for 6 weeks in male and female rats observed by Mullenix et al. (1995) proposed to address data need.

X(R[3]) EPA believes that there are not sufficient data on either acute or subchronic neurotoxicity of HF and maintains that this testing is needed. As an alternative, these studies could be performed via the oral route using NaF, if quantitative route-to-route extrapolation can be developed under an acceptable ECA. See Section 4 for additional details.

Developmental testing:

R-NaF[d] Route-to-route extrapolation of oral rat data base on NaF is proposed to fulfill this data need using studies by Collins et al. (1995) and Heindel et al. (1996). The proposal does not discuss how the need for second species testing will be addressed.

R-NaF[4] EPA believes that, under a satisfactory ECA and as an alternative to developmental toxicity testing, the developmental studies using drinking water exposures to NaF (Collins et al., 1995; Heindel et al., 1996) would provide adequate data on effect levels in the rat to serve as the basis for quantitative route-to-route extrapolation.

Reproductive testing:

R-NaF[4] Route-to-route extrapolation of oral data base on NaF proposed to fulfill data need: Messers et al. (1973) is a 2-generation reproductive study in mice; Tao and Suttie (1976) is a 3-generation study in mice; and an unpublished 2-generation study in rats cited in Sprando et al. (1996).

R-NaF[5] EPA believes that, under a satisfactory ECA, the proposed reproductive studies using oral exposures (drinking water, gavage, and diet) to NaF (Messers et al., 1973; Tao and Suttie, 1976; and Sprando et al., 1996) would provide adequate data on effect levels to serve as the basis for quantitative route-to-route extrapolation.

Immunotoxicity screen:

[f] No immunotoxicity testing was proposed. The epidemiologic data and the lack of histopathology on a previous 90-day study (Placke and Griffin, 1991) were cited as evidence for lack of potential immunotoxicity.

X[6] EPA maintains this proposed data need as stated in the proposed HAPs test rule and suggests it be a satellite study to the inhalation testing.

(4) EPA Comments on HF Panel Proposed PK Strategy

EPA has reviewed the proposal for a PK strategy to address the data needs for HF. This section provides detailed comments on the various components of the proposal. These comments include suggested changes that EPA believes should be made in order for the proposal to be found acceptable.

In general, EPA agrees with the proposed mode of action and dosimetry considerations pertinent to evaluating the testing requirements for HF. EPA agrees that the portal-of-entry effects of HF may be critical and limiting, and believes that the PBPK model could be used to confirm that circulating blood F^- levels after inhalation exposures to HF do not warrant concern for systemic effects. In addition to the available oral data on NaF, EPA believes that the toxicity data base compiled by the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) could aid in making these determinations since circulating F^- resulted from the metabolism of these chemicals. EPA also agrees with the proposed limited inhalation study, and believes that this study should be of 90-days' duration.

PK Model: EPA considers the proposed airflow modeling for inter-species dosimetry characterization to be state of the science, and an appropriate model structure to propose for a gas with an uptake efficiency of greater than 99% of the parent compound in the URT. EPA understands that the development of the portal-of-entry component of the PBPK model would be based on data for more than one concentration of a repeated inhalation exposure to ensure periodicity was attained. EPA also views that the proposal to develop the model for systemic F^- disposition on available NaF data is innovative and appropriate in order to perform route-to-route extrapolation of existing oral toxicity data.

EPA does not agree that the development of the systemic distribution model for F^- should be triggered only if histopathology is observed in the 90-day study. The objective of the PBPK model should be to provide a quantitative basis for extrapolating the existing oral data base on systemic effect levels. EPA maintains that the remote compartments model will need to be developed in order to confirm that the circulating blood F^- resulting from inhalation exposures is at or below that associated with effects from oral exposures to NaF for systemic endpoints. The model should be developed to simulate administration in drinking water for extrapolation of the developmental effects and diet or gavage for extrapolation of the reproductive effects. EPA further believes that compartments for the remote endpoints in question (e.g., brain, bone, fetal) may need to be explicitly developed depending on the blood concentrations after HF inhalation. In addition to the available oral data on NaF, EPA believes that the toxicity data base compiled by the PAFT could aid in making these determinations since circulating F^- resulted from the metabolism of these chemicals. EPA believes that human partition coefficients will be required for appropriate scale-up of the rat model.

Acute and Subchronic Toxicity testing: EPA believes that the submitted new data (Stonybrook, 1996) together with the previous acute study (DuPont, 1990) adequately address the histopathology and bronchoalveolar lavage (BAL) assay requirements. EPA notes that neither of these studies provides data on macrophage function. Since the demonstrated portal-of-entry effects of HF can involve changes in macrophage function, EPA believes that the macrophage function testing assay should be addressed as a satellite to the proposed inhalation testing. EPA also reasons that the Alarie assay may not provide

additional insights on either the mode of action or dose-response function since HF is already established as an irritant (e.g., a decrease in minute volume is suggested in Stavert et al., 1991). Therefore, under an acceptable ECA, EPA believes that the Alarie respiratory sensory irritation screen (ASTM E 981-84) may be superfluous since additional PK and mechanistic data would be obtained.

EPA can accept the proposed inhalation study with limited histopathology (URT, heart, spleen, liver, lung, and brain) and determination of plasma and urinary fluoride levels. EPA agrees that the proposed mapping of lesions in the URT, including severity scoring, will be useful to characterize the critical dose-response. EPA is concerned that the length of the proposed inhalation study was not specified in this PK proposal and brings to the attention of the HF Panel that EPA guidelines for subchronic testing require a 90-day treatment period. The minimum data base for derivation of an inhalation route reference concentration is a 90-day inhalation bioassay. EPA also calls attention to the provisions regarding URT histopathology in the Agency's upcoming health effects test guideline *TSCA Acute Inhalation Toxicity with Histopathology* as appropriate for application to this 90-day study. EPA agrees that the interim sacrifice design will provide insight on whether concentration (C), duration (t), or the (C x t) product is the dominant determinant of toxicity and, thus, on the appropriate dose metric. EPA suggests that a recovery component incorporated into this experimental design would help to ascertain if damage is cumulative (e.g., effect of concentration or duration on dynamics of repair).

Neurotoxicity testing: EPA does not agree with the Panel's interpretation and conclusions regarding the available neurotoxicity data and their proposed use to fulfill this data requirement. EPA believes that the *in vitro* data are of little use in the present discussion. These data, exemplified by the Nakagawa-yagi et al. (1993) study, show effects of HF (or F^-) only at concentrations in the millimolar range. EPA does not believe that these concentrations are relevant to the determination of residual risk. The HF Panel also asserted that a neurotoxicity study conducted according to the EPA guideline is not necessary due to the availability of data from the study by Mullenix et al. (1995), stating that the Mullenix method is capable of detecting effects that "...are simply too subtle to be among the kinds of effects that a standard neurotoxicology study has the precision to measure." EPA believes that this statement is without scientific basis. EPA has no knowledge of systematic studies comparing the Mullenix method with the standard neurotoxicology battery (see also Ross and Daston, 1985). Furthermore, the neurotoxicology battery has undergone extensive and international validation studies, whereas there is no published record of validation of the Mullenix method. EPA maintains that the database of available information on the neurotoxicity of HF is currently deficient and that acute and subchronic neurotoxicity evaluations are required.

EPA believes that the effect levels and associated F^- levels available from the inhalation data base compiled by the PAFT may aid in determining inhalation exposures of HF potentially associated with neurotoxicity since Neurotoxicity testing was performed by PAFT and circulating F^- resulted from the metabolism of those hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs) tested. EPA also believes that simulation exercises, utilizing the PBPK model, to predict internal concentrations of F^- after inhalation exposures that can be compared to internal concentrations achieved at effect levels associated with portal-of-entry and other systemic toxicity would be informative to gauging the potential for neurotoxicity after

inhalation exposure. Additionally, EPA concludes that, as an alternative, neurotoxicity studies could be performed using NaF via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA.

Developmental toxicity testing: EPA believes that, under an acceptable ECA, the proposed developmental studies using drinking water exposures to NaF conducted in rats by Collins et al. (1995) and in rats and rabbits by Heindel et al. (1996) would provide adequate data on effect levels to serve as the basis for quantitative route-to-route extrapolation. EPA understands that quantitative route-to-route extrapolation would require characterization of the uptake for the respective oral administration method (i.e., drinking water) and calculation of inhalation exposures that would result in the same internal dose measure. EPA notes that the HF Panel proposal does not address how the second species testing requirement identified in the proposed HAPs test rule will be met since model development is only proposed for one species (rat).

Reproductive toxicity testing: EPA believes that, under an acceptable ECA, the existing reproductive studies using oral exposures (drinking water, gavage, and diet) to NaF (Messers et al., 1973; Tao and Suttie, 1976; and Sprando et al., 1996) would provide adequate data on effect levels to serve as the basis for quantitative route-to-route extrapolation. EPA understands that quantitative route-to-route extrapolation would require characterization of the uptake for the respective oral administration methods (i.e., drinking water, gavage, and diet) and calculation of inhalation exposures that would result in the same internal dose measure in the appropriate test species (i.e., mouse and rat).

Immunotoxicity screen: EPA does not consider either the cited epidemiologic data nor the lack of histopathology as sufficiently sensitive to use as a screen for potential immunotoxicity. Furthermore, the potential for immunotoxicity is not precluded on the basis that portal-of-entry effects are dominant since the immune system is multi focal (e.g., circulating cytokines or antibodies could have secondary systemic immune effects). EPA believes that this data need remains a concern and can be addressed as a satellite SRBC assay to inhalation testing.

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(6) PK Proposal Review Staff

The following table lists individuals who contributed in the preparation of EPA's preliminary technical analysis of the Chemical Manufacturers Association's Hydrogen Fluoride Panel PK proposal for hydrogen fluoride.

PK Proposal Review Staff

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APPENDIX IV

HF HAPS GROUP SEPT. 10, 1997, REPLY TO EPA RESPONSE TO ALTERNATIVE TESTING PROPOSAL

CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
VICE PRESIDENT
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September 10, 1997

Charles M. Auer, Director
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Re: Alternative Testing Proposal on Hydrogen Fluoride:
EPA Hazardous Air Pollutants (HAPs) Testing Initiative
(OPPTS- 42187A: FRL-4869-1)

Dear Mr. Auer:

This letter is submitted on behalf of the members of the CMA Hydrogen Fluoride (HF) Panel and the HF HAPs Group, referred to collectively as the Panel in response to your letter of June 26, 1997. The Panel has reviewed EPA's response to our proposal (submitted to EPA on November 22, 1997) for alternative testing of HF to satisfy most of the testing required in the proposed HAPs test rule. Overall, we are pleased with the favorable review to this proposal by EPA scientists, and are willing to proceed toward an Enforceable Consent Agreement (ECA). There are, however, several principle issues for continued discussion with EPA before entering into an ECA.

Acute Toxicity Testing

We acknowledge that the Stoneybrook (1996) study satisfies the proposed test rule for acute toxicity testing. However, the Panel disagrees that macrophage function is needed for the risk assessment intended to be conducted by EPA. Macrophage function analysis is valuable in screening studies as a measure of lung injury. However, given the extensive acute toxicity data available on HF, including the Stoneybrook study, the conduct of this analysis would not provide additional useful information.

PBPK Model and Subchronic Toxicity

The HF Panel is pleased to receive a supportive response from EPA regarding the proposal to conduct a repeated exposure inhalation toxicity study on HF that will include detailed histopathology of the upper respiratory tract (URT), limited histopathology of the lung and systemic organs (e.g. heart, spleen, liver, and brain) and measures of plasma fluoride. The detailed histopathology of the URT,

coupled with computational fluid dynamics modeling of the URT, will enable the development of alternate dose metrics, e.g. HF flux estimates, useful for interspecies extrapolation.

EPA has stated that the minimum data base necessary for derivation of a reference concentration includes an inhalation study of 90-days duration. Although the HF Panel agrees with EPA that health risk assessments must be based on adequate toxicity data in order to reduce the uncertainty in these assessments, *a priori* decisions on the length of exposure period without regard to chemical-specific issues does not seem appropriate. In the case of HF, the mode of action, as described in our PK proposal, suggests that toxicity to the URT from HF exposure will be dominated by exposure concentration rather than duration. We believe that a study of 28-days duration, with multiple interim sacrifices, should be adequate and is more appropriate.

EPA suggested that the inhalation toxicity study include a recovery group in order to ascertain if damage is cumulative. Given that the tissue responses of the URT during the repeated exposure will be in a dynamic balance between cytotoxicity and repair, the multiple sacrifices planned for the inhalation study are likely to provide insight to the effect of concentration or duration on the dynamics of repair. It is not clear to the Panel how recovery data would be used in the risk assessment for HF. However, we are open to discussing this with EPA and may consider this proposal if EPA can illustrate how data on tissue repair will be used in the risk assessment process.

EPA disagreed that the development of the systemic distribution model for fluoride should be triggered only if histopathology is observed in a repeated inhalation study. The reason was that the objective of the PBPK model should be to provide a quantitative basis for extrapolating the existing oral data based on systemic effect levels. The Panel believes that an iterative approach, in which development of the systemic PBPK model would be triggered by observation of systemic toxicity, is a prudent use of resources and remains as our proposal. It would not be necessary to develop such a model if the risk assessment is ultimately based on the URT toxicity as we expect. Our position is not to discount the development of the systemic PBPK model, only that the need for its development be determined based on the results of the inhalation study. Similarly, if plasma levels of fluoride measured in the inhalation study are below the maternal plasma fluoride NOAELS from the developmental toxicity studies in rabbits and rats (Heindel et al., 1996; Collins, et al., 1995), then there would be no point in developing a PBPK model that estimates fetal exposures to fluoride. Further, the model could allow species-to-species extrapolation, thereby obviating a need for a second species developmental toxicity study.

Neurotoxicity

The Panel is concerned that EPA disagreed with the Panel's logic to omit a neurotoxicology study. The Agency states that there is no scientific basis for the

Panels statement that the effects described by Mullenix et al. (1995) "were simply too subtle to be among the kinds of effects that a standard neurotoxicology study has the precision to measure." The Panel continues to believe that its statement is valid. Although the Agency is correct in pointing out that there has not been a scientific comparison of the method employed by Mullenix et al (1995) with the methods of a neurotoxicity study conducted under EPA guidelines, a strict comparison is not necessary to reach a meaningful conclusion about relative sensitivity.

The Agency is correct in stating that the guideline methods have been the subject of international inter-laboratory comparisons (Mosher and MacPhail, 1997). The Agency should not make the existence of such comparisons a necessary condition for acceptability of scientific data. The Panel notes that the Agency did not regard such trials as necessary for regulatory submissions of guideline studies prior to the conduct of the lab-to-lab comparisons. The important point is that the Agency should not reject the results of a scientific study because it does not happen to conform with guidelines. Instead, each study should be evaluated on its own merits.

Immunotoxicity

EPA states that epidemiological data and the lack of histopathological and clinical chemical effects are not sufficient to avoid the conduct of an immunotoxicity assay. However, the Panel notes that the conduct of any toxicity study for an existing chemical substance should be done because data are suggestive of a possible effect. With HF, exposure to inhalation does not produce effects that would suggest that the immune system is a target system. Therefore, the Panel continues to believe that conducting an immunotoxicity study is inappropriate.

The Panel appreciates the Agency's review of its alternative testing proposal for HF and welcomes this opportunity to work with EPA on developing an ECA. We look forward to meeting with you and members of your technical staff to initiate this process. In the meantime, if you or members of your staff have questions or would like additional information, please do not hesitate to contact Elizabeth Festa Watson, the Panel Manager, at 703-741-5629.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

References attached

cc: OPPT Docket Clerk (3 copies)

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